Volume 18, Number 5
NOVEMBER 1955

Postgraduate Medicine

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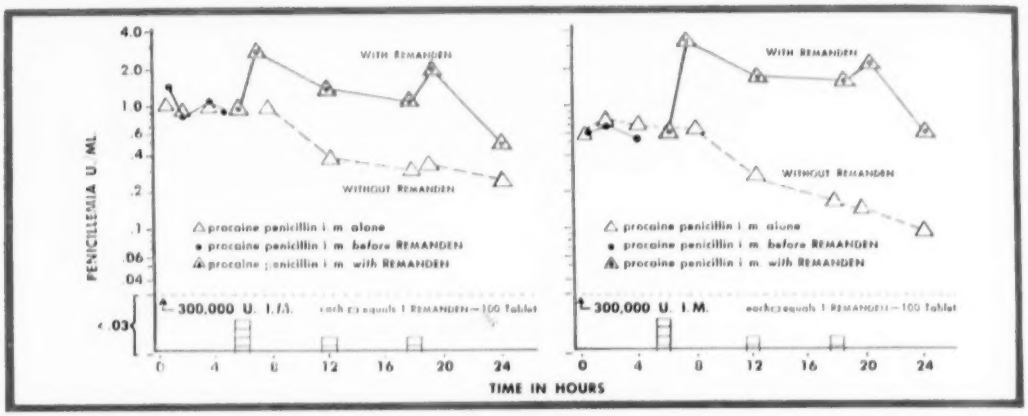

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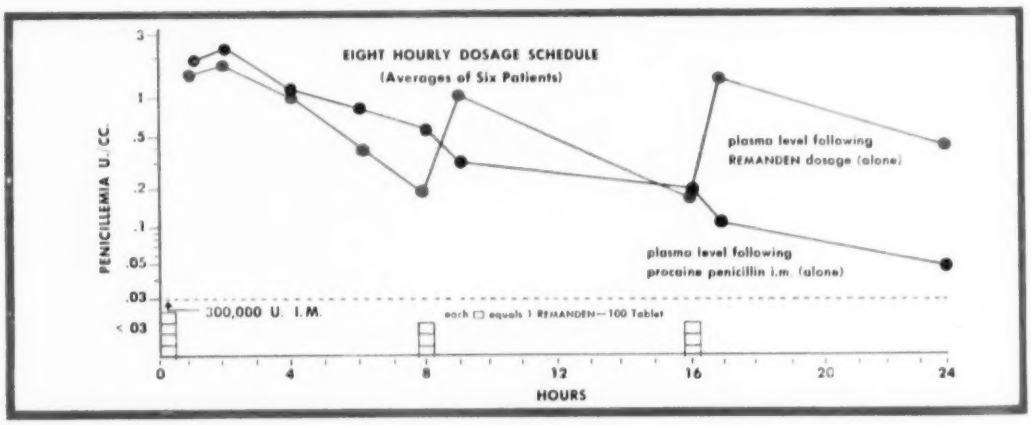

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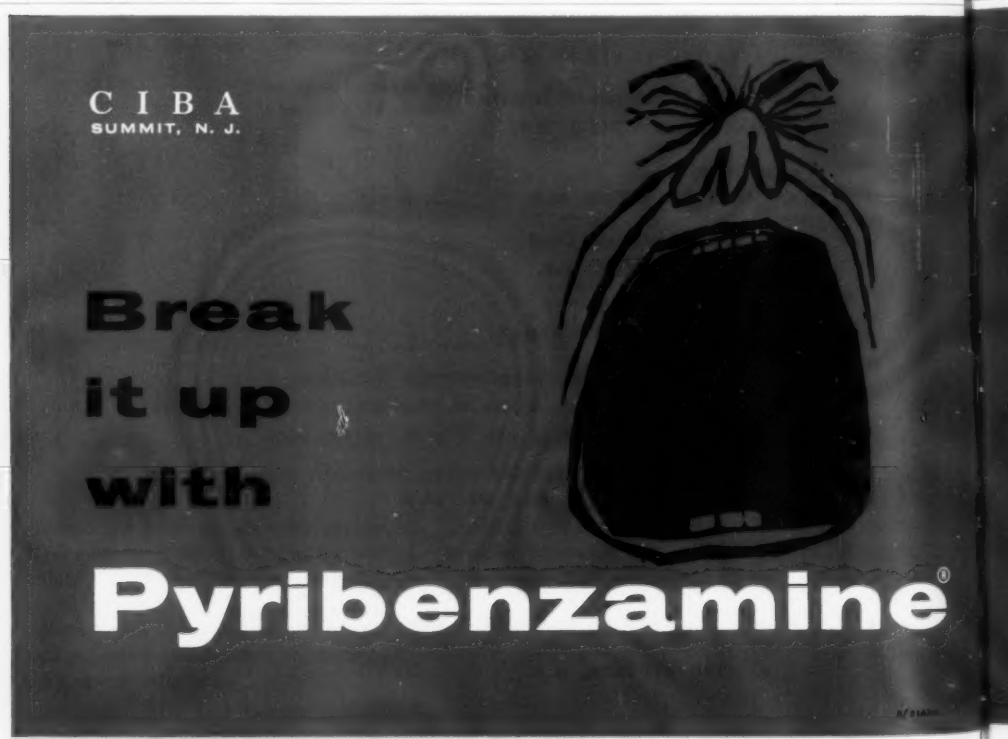

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IN Postgraduate Medicine

JANUARY 1956

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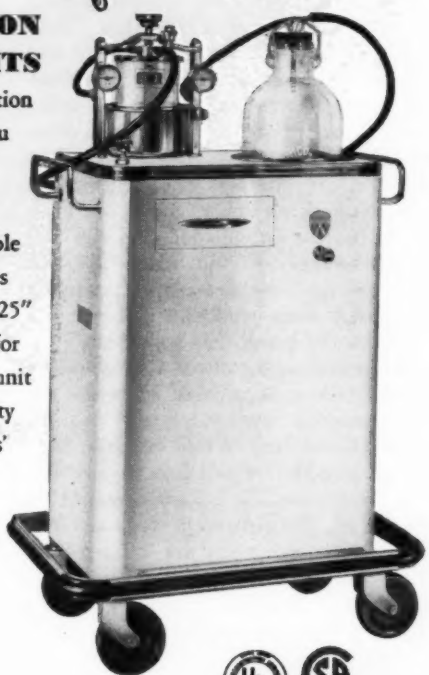

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Your Questions answered

Readers may send questions from their own practice or other medical problems which will be answered by qualified consultants. Replies are forwarded by mail immediately and selected questions and answers are published each month in this section.

• STERILITY TREATMENT

Q. A 40 year old nulliparous, infertile woman complains of sterility and amenorrhea. Menstruation began when she was 15 years old and was normal for one year, after which time there was severe dysmenorrhea and abdominal colic. The menstrual blood was dark and clotted. After treatment she menstruated normally for about five years until she married. After intercourse she said her genitals felt inflamed, and she menstruated twice within one month. This was followed by amenorrhea and she was believed to be pregnant, but this was later proved false. She and her husband both complained of maculopapular rash on the hands. She was treated for the amenorrhea and menstruated regularly while receiving medication. At present, however, she has been menstruating once every 6 to 12 months.

Her general health is good and her only complaint is her sterility, which has caused her husband to divorce her. He has since remarried and had children. The patient is stout and has normal sex characters except for an infantile uterus, and results of the Wassermann test were questionable. Her fallopian tubes are patent.

What treatment is suggested for her sterility? Should a hormone combination be tried? The patient would have a chance to remarry if menstruation were normal.

M.D.—Iraq

A. This patient quite obviously has an endocrine imbalance. Basal metabolic rate should be determined and thyroid dosage adjusted accordingly. DEXEDRINE® or some other appetite depressant should be given to reduce weight.

In addition, I would suggest the administration of 3 mg. diethylstilbestrol daily. Progesterone, 25 mg. daily, should be given intramuscularly 23, 24 and 25 days after beginning diethylstilbestrol. The diethylstilbestrol dosage should be repeated, and at least three successive cycles should be induced with the progesterone therapy at four week intervals. If menstruation is not induced by this plan, therapy should be continued for three additional months. If there is no response after this time, there are no further suggestions.

• SCLEROSING HEMANGIOMA

Q. A 23 year old white woman has recurrent attacks of pain, swelling, ulceration and, after healing, brown pigmentation of both ankles. The first episode occurred six years ago during the summer, and the condition persisted until fall. Each summer since then the condition has recurred, necessitating complete bed rest. If the patient remains off her feet, the lesions do not ulcerate. After four episodes, she was sent to a large and reliable diagnostic center in New York. A complete work-up was carried out; in fact, she was presented at a dermatologic convention. Three possible diagnoses were proposed, but all

(Continued on page A-26)

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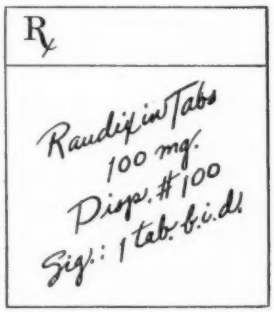

*Ataractic, from ataraxia: calmness untroubled by mental or emotional excitation. (Use of term suggested by Dr. Howard Fabing at a recent meeting of the American Psychiatric Association.)

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were ruled out when the results of pathologic study of the specimens obtained with skin biopsy were found not to coincide with the clinical findings. The three possible diagnoses were (1) angioblastoma, (2) lupus erythematosus and (3) purpura annularis telangiectodes (concomitantly—tinea versicolor).

I saw the patient for the first time four weeks ago, when a new phase had entered the clinical picture, i.e., an area of numbness had developed suddenly on the anterolateral aspect of the left shin, extending from four inches below the knee to an inch above the ankle and about six inches wide. Also, for the first time there was pain in the great toe of the left foot.

Following the work-up two years ago, a course of cortisone therapy had been administered because the pathologic report indicated acute arteriolitis of unknown etiology, but this treatment did not alter the clinical course. In fact, the side effects necessitated discontinuing the drug.

I subsequently forwarded the biopsy slides to the pathologist who trained me, and his diagnosis is sclerosing hemangioma. Before I received his report, I had instituted the following therapy: (1) daily intramuscular injections of vitamin B_{12}, 1000 micromilligrams; (2) daily intramuscular injections of MY-B-DEN® (brand of adenosine 5-monophosphate), 25 mg.; (3) 1200 mg. vitamin C and 240 mg. rutin daily, orally; (4) riboflavin orally, 30 mg. daily; (5) modified whirlpool baths for the pain and numbness; (6) Buerger's exercises.

Assuming the diagnosis of sclerosing hemangioma is correct, please advise whether this therapy is appropriate and offer alternate treatment.

M.D.—New York

A. In a case of a young woman with painful swellings with ulcerations on the ankles, one must always think of tuberculosis (erythema induratum, or Bazin's disease). In older persons, past 40 years of age, one must think of nodular vasculitis, which is a vascular, inflammatory reaction around the vessels of unknown etiology.

The diagnosis of sclerosing hemangioma, I think, goes along more with nodular vasculitis.

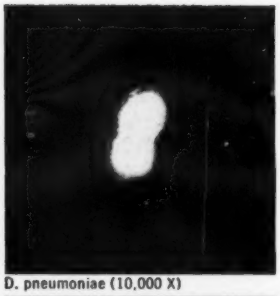
The best treatment for this disease is, of course, elastic bandaging to support the blood supply. I cannot suggest any better therapy than that which already has been instituted.

Second consultant: From the clinical history given, there is no evidence of sclerosing hemangi-

(Continued on page A-28)

The organisms commonly involved in

Bronchopneumonia



D. pneumoniae (10,000 X)

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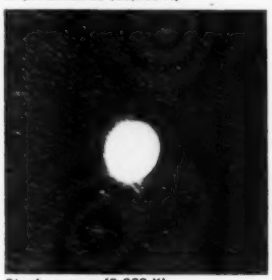
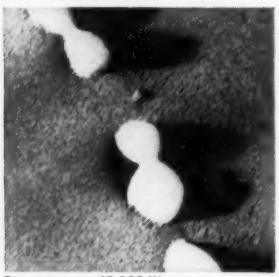


Staph. aureus (9,000 X)



Str. pyogenes (8,500 X)

H. influenzae (16,000 X)

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oma in spite of the pathologic report. The eruption as described appears to fall into that rare group which consists of livedo reticularis together with summer ulcerations which are frequently of the infarctive type.

Treatment should consist of supportive bandages and a hexamethonium type of drug. Occasionally sympathectomy has been of help, but the above should be tried first. It is quite satisfactory to continue with whirlpool baths.

• ARTERIOSCLEROTIC CHANGES

Q. In over 100 postmortem examinations, chiefly on geriatric patients, I have noted the following distribution of arteriosclerotic changes: In the aorta, I have found syphilitic aortitis, with sclerosis greatest in the ascending aorta and the arch of the aorta; in the coronary arteries, the sclerosis is usually greatest in the proximal segments of the vessels. Is there any explanation?

Is medionecrosis of an artery a separate disease entity from arteriosclerosis, and, if not, could it be caused by arteriosclerotic changes in the vessel? If they are separate entities, which process is most frequently responsible for aortic aneurysms, excluding syphilitic aortitis.

M.D.—Ohio

A. Your observations conform to statements found in recent textbooks on pathology. In "Pathology" (Philadelphia, Lea & Febiger, 1955), Dr. Peter Herbut states on page 236, "Syphilitic aortitis . . . is most severe in the first part of the ascending aorta . . . for some unexplained reason the inflammation seldom extends below the level of the diaphragm." In the discussion of pathologic changes in coronary arteries, he states (page 201), "Although all portions of the coronary arteries may be affected, the proximal portion of the anterior descending branch of the left coronary artery is most commonly involved." The cause is not yet known. Changes in serum lipids and lipoproteins and local factors in the arterial wall have been suggested as factors.

Medionecrosis, also called idiopathic cystic medionecrosis, is an entity in which there is mucoid degeneration of the media of the aorta and larger arteries. This predisposes to the formation of dissecting aneurysm, usually of the ascending aorta, descending inferiorly, even to the femoral arteries. In the abdominal aorta nine-tenths of all aneurysms are arteriosclerotic.

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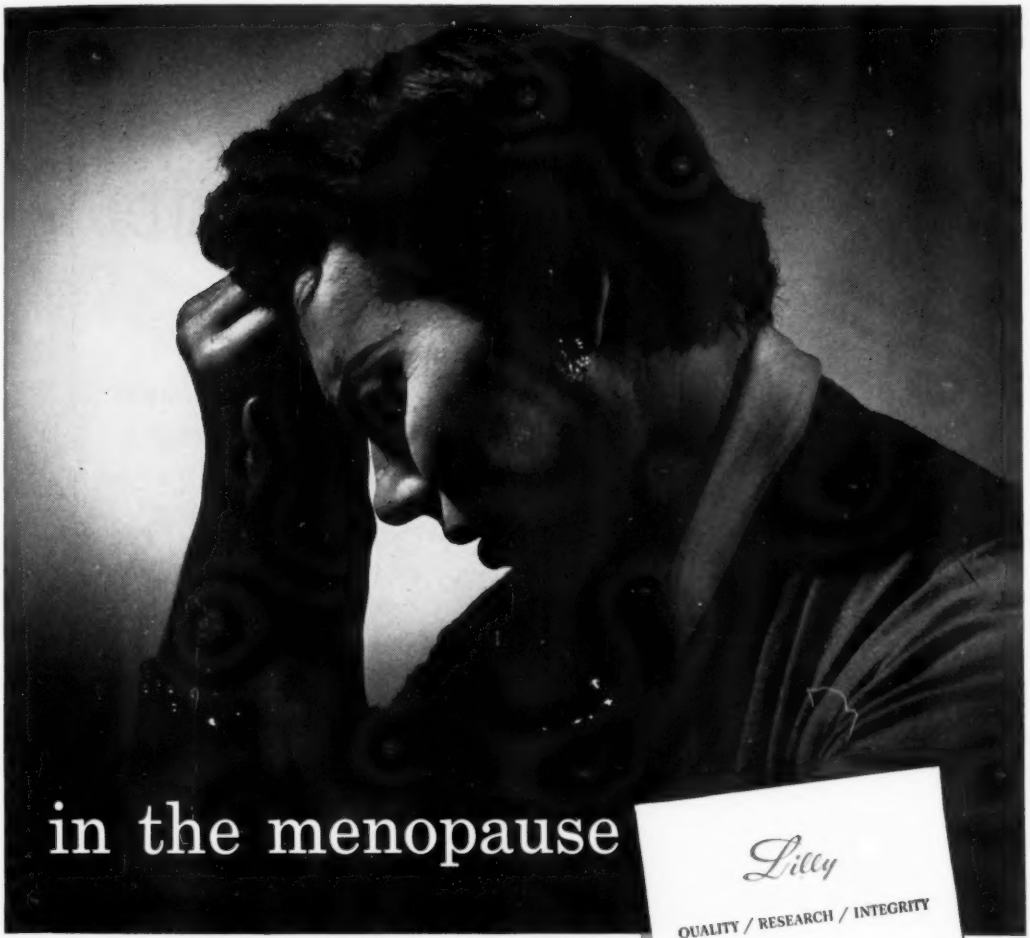

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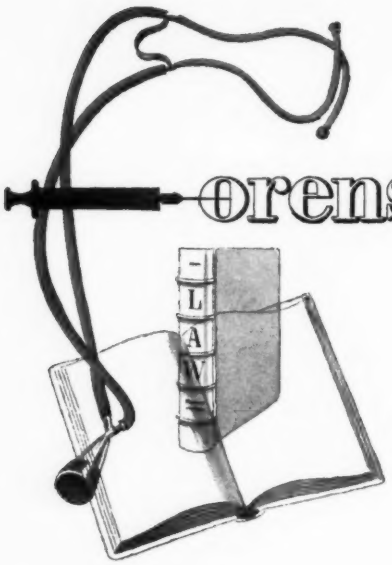

Forensic Medicine

Editors

Dr. Thomas A. Gonzales
Dr. Milton Helpern
Dr. Samuel A. Levinson

The Industrial Hazards of the Organic Phosphates

WILLIAM E. B. HALL*

Chambersburg, Pennsylvania

WILLIAM
E. B. HALL

THE organic phosphates are a group of chemicals that promise great benefit to mankind, but in the hands of the careless, ignorant or uninstructed they can be deadly dangerous. Because of their recent and widespread use as insecticides in agriculture, it is becoming mandatory that the medical man, particularly in agricultural areas, become thoroughly acquainted with these substances, their uses and modes of action, recognize the signs and symptoms of intoxication due to these phosphates, and be familiar with the means of treatment of poisoning by them. Within the past eight years, an increasing number of articles on the organic phosphates have appeared in the medical literature, dealing particularly with their pharmacology. Between January 1951 and December 1954 the "Current List of Medical Literature" of the Armed Forces Medical Library listed over 268 papers on these topics.

The organic phosphates are esters of phosphoric acid, nearly colorless and odorless liquids or gases, and possess, in common, one or more phosphate radicals in their formulas. All are dangerous as extremely potent inhibitors of cholinesterase activity.

Uses of the Organic Phosphates

Working with the alkyl phosphates, Lange and von Kreuger[1] first noted the high toxicity of the organic phosphates. This led to their applications by the Germans as nerve poisons and nerve gases.[2] Today they are recognized as the only really effective potential long-range weapons

(Continued on page A-36)

*The Chambersburg Hospital, Chambersburg, Pennsylvania.

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available in chemical warfare, and this projected applicability is now universal.

Certain of these phosphates have had a limited medical use. The dialkylphosphates[3,4b] and the alkyl fluorophosphates[5] including di-isopropyl fluorophosphate (DFP)[4c,5] have been used in treating urinary retention, glaucoma, abdominal distention and myasthenia gravis. Tetraethylpyrophosphate (TEPP)[3,4a,5] has also been used in therapy of myasthenia gravis. The use of DFP and others has resulted in only partial success, as even ineffective doses may cause serious side effects, such as nausea and vomiting, dizziness and fainting. In general, these phosphates have met serious limitations due to very narrow margins between the effective therapeutic and the toxic doses.

Organic phosphates do not all exhibit identical toxicity. Recently an organic phosphate has been developed with minimal toxic effect on mammalian life, including man. This substance, known as malathion[6], has found important use in combating flies, plant lice and aphids. It is to be expected that other organic phosphates soon will be developed to afford fully safe broad-spectrum protection in agriculture against insect pests.

The Organic Phosphates

The phosphate esters are widely used as insecticide sprays, the one most commonly used being parathion (O, O-diethyl O-*p*-nitrophenyl monothiophosphate). The chemicals are usually liquids, but are used in sprays and wettable powders. Parathion in almost pure form is a brown to yellow liquid. It comes to the user, however, as a 25 per cent wettable powder, and is made up for use as a spray or mist of 1 per cent or less, or as a dust of 2 per cent or less. Water, including alkaline washes such as soap and water, results in active hydrolysis and detoxication of spray deposits.

The organic phosphates in common use are: (1) dialkylphosphate;[3,4b] (2) malathion;[6] (3) parathion; (4) hexaethyltetraphosphate (HETP);[3,4a,d] (5) ethyl *p*-nitrophenyl thionobenzenephosphate (EPN);[3] (6) octomethyl pyrophosphoramide (OMPA);[3] (7) di-isopropyl fluorophosphate (DFP).[3,4a,6] Each has its particular mode of use and application, and each has its particular danger.

Physiologic Action

The outstanding student of the organic phos-

(Continued on page A-38)

Angina pectoris prevention

Most efficient of the new long-acting nitrates, METAMINE prevents angina attacks or greatly reduces their number and severity. Tolerance and methemoglobinemia have not been observed with METAMINE, nor have the common nitrate side effects such as headache or gastric irritation. Dose: 1 or 2 tablets after each meal and at bedtime. Also: METAMINE (2 mg.) with BUTABARBITAL (¼ gr.), bottles of 50. THOS. LEEMING & CO., INC., 155 EAST 44TH STREET, NEW YORK 17, N.Y.

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phates has been Grob[7] of Baltimore, who has made extensive studies of their pharmacology and physiologic effects. The organic phosphates, including parathion, act as irreversible inhibitors of cholinesterase. This inhibitory effect resembles that produced by physostigmine except that inhibition by the latter is actively reversible. Normally, cholinesterase controls by hydrolysis the accumulation of acetylcholine in the body. Acetylcholine is important in the transmission of nerve impulses to voluntary and involuntary muscles, and has a potent effect on the parasympathetic nervous system. Removal or neutralization of cholinesterase by any means results in serious accumulations of acetylcholine, producing toxic effects resembling the combined effects of nicotine and muscarine. This is the picture in poisoning by the organic phosphates. In excessive doses, a curarelike flaccid paralysis results. These toxic effects develop when the tissue levels of cholinesterase drop to about 30 per cent of normal. Recovery occurs only if life is maintained sufficiently long to afford regeneration of new cholinesterase above the critical low level.

Skin and ocular lesions do not develop from contact. Acquired tolerance or sensitivity to these compounds is not known. However, effects of even minimal doses can be potentially additive, if acquired before the return of normal cholinesterase levels.

Routes of Entry Into the Body

The organic phosphates, including parathion, may enter the body through any portal and in any physical state, commonly by inhalation or swallowing. Absorption is active through the conjunctiva, and fatalities in humans actually have occurred from absorption through the intact skin.

Professional and Accidental Poisoning Contacts

Toxic symptoms from the organic phosphates may develop from direct contact with the original chemical or its powders, dusts and sprays, or indirectly from contact with sprayed unwashed objects as much as 30 days after the original spraying. Dusting apparatus, plants and vegetables are important sources of contact. As these chemicals may be sprayed or distributed by airplane, they constitute a serious occupational hazard to aviators. They are a constant danger

(Continued on page A-39)

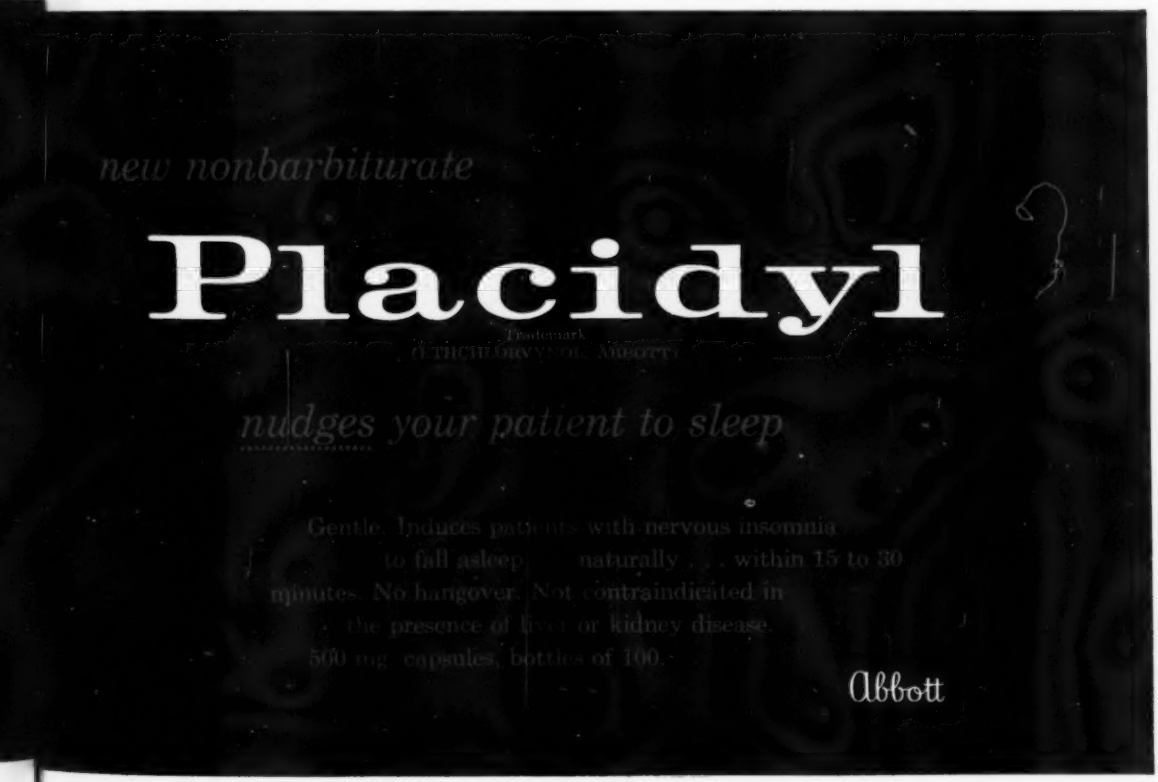
to manufacturers, packagers and distributors and to the worker preparing the final dilution sprays or powders for use. Operators and maintenance men of spray equipment share contact hazards with workers in nurseries, greenhouses and agricultural pursuits. There may even be ingestion of the chemicals on recently sprayed foods and fruits that have not been properly washed. Workers on other jobs, travelers, bystanders and occupants of homes in or near treated areas may receive contact, especially if windward of the spraying. Children playing or wandering unguarded in the sprayed areas may receive dangerous contacts. These chemicals may even be a danger source to beekeepers, though injury is usually financial from the serious depredations of these chemicals on the bee population which may accidentally serve or reach sprayed flowering orchards.

Dosages in Acute Intoxication

The exact minimal lethal dosage in organic phosphate poisoning, including parathion poisoning, has not been established, but deaths have occurred from apparently minor contacts. Inhalation of small amounts of spray and splashing with 1 per cent spray suspensions, insufficient to soak the skin, have been fatal. Ignorance of foreign workers and handlers of these chemicals has been responsible for a considerable incidence of fatal poisonings, much in excess of the reported fatalities in the United States. From animal experimentation, it would appear that the fatal dose of parathion in man is probably between 12 and 20 mg. (1/5 to 1/3 gr.).

The onset of toxic symptoms may occur anywhere between a few minutes and 24 hours after exposure. Such exposure may be delayed until the end of the day's work when the worker may be changing his contaminated clothing, or may be as much as 30 days after spraying, with ingestion of unwashed fruits. Most commonly, symptoms first appear within 30 minutes or at night in bed. The acute emergency lasts 24 to 48 hours, but the blood cell levels of cholinesterase are restored at the rate of 1 per cent of original activity per day. During this asymptomatic period, pending full restoration of cholinesterase, an acute attack may be precipitated on even a very minor contact. Throughout this period, then, there should be complete shielding or withdrawal from possible contacts with the phosphates.

(Continued on page A-40)



Dosages in Chronic Intoxication

Chronic intoxication occurs only in terms of depletion of cholinesterase and the additive effects of repeated small doses before full recovery of the body cholinesterase. Once this recovery occurs, there is no permanent anatomic or physiologic damage or increased susceptibility to further contacts.

Signs and Symptoms in Man

The signs and symptoms of intoxication are referable to the nicotine and muscarinelike effects, with action on the parasympathetic and central nervous systems and the voluntary muscles, especially those used in respiration. The premonitory symptoms are headache, giddiness, profuse sweating, tears and excessive salivation and bronchial secretions. Within 30 to 60 minutes, these are followed by nausea and vomiting, cramps, diarrhea and chest discomfort. Dropping blood pressure and muscle twitching appear. Loss of reflexes and sphincter control, respiratory paralysis, convulsions and coma are late signs, but recovery may still occur if treatment is instituted promptly and thoroughly and is well maintained. Complaints of giddiness and blurring of vision are very important diagnostically and may occur quite early. Pinpoint pupils are an important observation.

Laboratory Findings

There are no material changes from the normal to be found with the most exacting of laboratory examinations except for the depression of the blood, serum or tissue cholinesterase levels. The technic or method of Michel[8,9] is widely used in determining the blood cholinesterase levels, based on the end-point blood pH levels. This method affords routine testing of workers, finger tip blood samples being the only source material required. The United States Public Health Service uses a more exact though less serviceable manometric method. Many other methods and variants have been developed for detection and quantitative determination of the intoxicants and their bodily effects.

There is a similar lack of material abnormal effects at autopsy except for the severely altered cholinesterase levels. Pulmonary edema will be observed, together with the effects of asphyxia and convulsions. Tissue concentrations of parathion may be determined by the method of Averell and Norris,[10] modified by Lehman.[11]

(Continued on page A-42)

asthma

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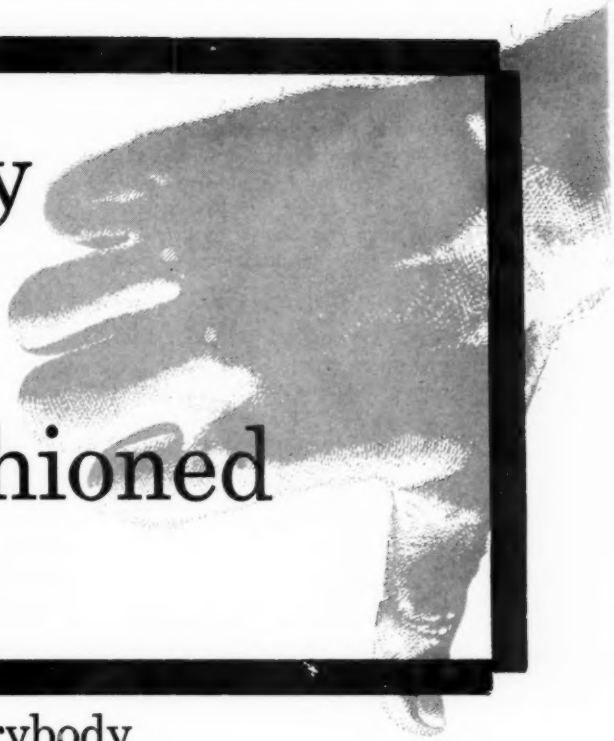

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Diagnosis of Intoxication

Any patient with a history of exposure to any of the organic phosphates, and presenting any of the afore-mentioned signs and symptoms, particularly headache and *fixed, contracted pupils*, warrants a presumptive diagnosis of organic phosphate poisoning. Treatment should be started immediately, and not delayed pending determination of blood cholinesterase levels. Other laboratory diagnostic tests are useless.

Treatment

Prompt and energetic treatment is required, consisting of large doses of from 1 to 2 mg. of atropine sulfate every hour, up to 10 to 20 mg. per day, especially for respiratory embarrassment. This dosage varies considerably according to the various writers. Flint[3] mentions 1/60 to 1/30 gr. (0.001 to 0.002 gm.) per subcutaneous injection. Governmental services advise prompt taking by the worker of two atropine tablets, each of 1/120 gr. (1.5 mg.), and immediately calling the doctor for skilled care of the poisoning. Intravenous administration of atropine may be preferred. In severe cases with deep anoxia, however, atropine may be dangerous. It has been observed[12] experimentally that the resultant release of the heart from vagal control causes increased cardiac activity which in the presence of severe anoxia may lead to immediate ventricular fibrillation and death. Treatment with atropine, then, should defer to adequate ventilation of the lungs.

Oxygen is urgently required and artificial respiration may be needed. Constant vigilance for 24 to 48 hours must be maintained, as relapse is not uncommon. Teams skilled in methods of artificial respiration, or an artificial respirator, should be available constantly. Bronchial secretions should be removed by aspiration, tilting or intratracheal tube. In case of ingestion, the stomach should be evacuated by forced vomiting and lavage with warm water.

The contaminated clothing of the patient should be removed and the body washed with soap and water, although alkaline washing soda is preferred as it more actively hydrolyzes the parathion. Persons handling or examining the patient and his clothing must observe full self-protection, including the use of surgical gloves to prevent skin contamination. As soon as safety warrants, the patient should be transferred to a hospital, accompanied by persons prepared to

(Continued on page A-43)

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institute or maintain any emergency treatment indicated by further developments.

In warning, *morphine sulfate*, codeine sulfate, DEMEROL® or large doses of barbiturates *must not be given*, even for muscular twitching or convulsions. These signs too promptly lapse into flaccid paralysis in this intoxication, with respiratory suspension and profound anoxia. If sedation is necessary, Flint[3] advises giving chloral hydrate orally or intramuscularly, or paraldehyde orally or intramuscularly in the smallest effective doses. We are also to be warned against the use of apomorphine hydrochloride or ipecac as an emetic, or calcium gluconate as an anticonvulsant. Sodium thiosulfate, magnesium sulfate and potassium permanganate have also been contraindicated.

Prognosis

The prognosis is good if the condition is recognized early and emergency treatment is instituted promptly. Otherwise the outlook is quite serious. Even with severe exposure, progressing even to convulsions and coma, there may be recovery if the patient is given energetic, continuing therapy. With recovery, there are no residual or permanent effects. This depends entirely on the body cholinesterase levels and the subsequent regeneration of autogenous cholinesterase to normal levels.

Prevention

Manufacturers[9] and government services[6, 13] have many bulletins on the recognition of the industrial-agricultural pesticides and methods for their handling and for prevention of poisoning. These may be summarized as follows:

1. In handling parathion and other organic phosphates, the worker must avoid breathing the wettable powder while opening the bags and introducing it into the spray tanks, and avoid inhaling the spray mist during the spraying operations. He should work to the windward while handling the wettable powder and sprays, and should wear an *approved* (U. S. Bureau of Mines) respirator at all times when working with these materials or when spraying or entering sprayed areas.

2. The hands, arms and face should be thoroughly washed after handling the phosphates, including parathion, and *before* eating, drinking or smoking. There should be a thorough bath, preferably a shower.

(Continued on page A-44)

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3. Under all conditions involving spray, mist or dust, protective clothing should be worn, such as a plastic raincoat and plastic hat.

4. Parathion wettable powder or spray should never be handled with the bare hands. If handling is necessary, natural rubber gloves should be worn—never synthetic rubber, leather or cloth gloves.

5. During spraying or washing, care should be observed not to contaminate streams, ponds or water supplies. Empty bags and containers used in shipping or mixing the powders or sprays should be burned or buried.

Two other rules could be added:[5]

1. All workers should be thoroughly instructed in the dangers of the chemicals and the proper methods of handling. The careless, the daredevil and the unintelligent worker should have no part in this type of labor.

2. All workers should be taught the early signs and symptoms of this poisoning and be impressed with the need to stop work immediately and to seek medical aid promptly.

Managers of farms using parathion or other organic phosphates should have on hand a supply of atropine for emergency treatment of these poisonings. As atropine itself is a poison, it can be secured only on a doctor's prescription. It is to consist of a supply of atropine sulfate in tablets or capsules of 1/120 gr. (1.5 mg.). This atropine should never be used as a prophylactic as this may obscure signs of serious intoxication. Atropine should be given only *after* warning signs or symptoms appear, pending arrival of medical care.

Conclusion

With the exception of malathion, the organic phosphates, including parathion, are highly toxic agricultural insecticides, related to and acting like the nerve gas poisons which have been developed as agents for chemical warfare. These substances neutralize the body cholinesterase, causing toxic accumulations of acetylcholine, with resultant effects resembling muscarine and nicotine poisoning. Intoxication is identified in the living patient by a characteristic chain of signs and symptoms, including fixed, contracted pupils. Laboratory tests show solely a depression of the cholinesterase levels, and this is also the sole diagnostic finding at autopsy. The industrial worker, the physician and the forensic investigator should all be conversant with the prevention, recognition and the treatment of intoxications from these very valuable but potent agricultural chemical weapons.

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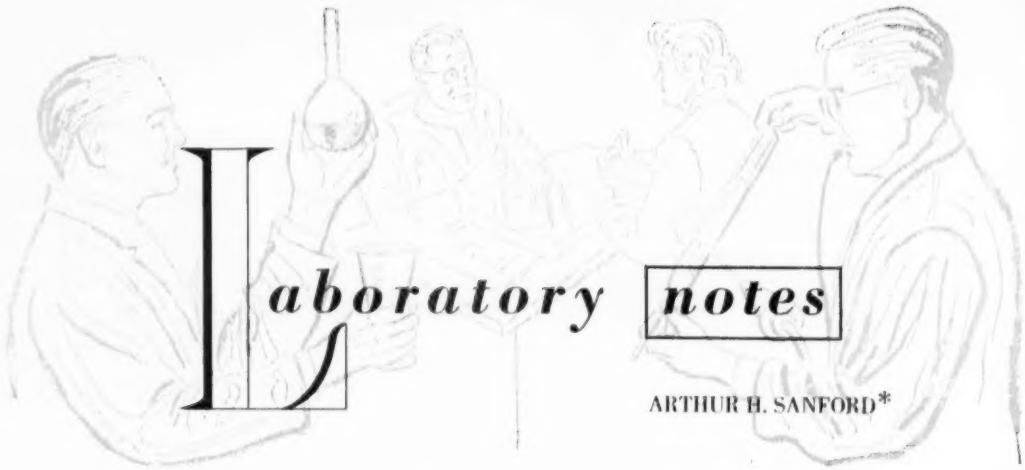

Laboratory notes

ARTHUR H. SANFORD*

"Pharyngealconjunctival Fever"

LAST January I received a letter from a friend describing what may have been a new virus disease, inasmuch as several persons in that community seemed to have similar symptoms.

The letter stated: "My current illness started with a severe sore throat, with very much inflamed and swollen glands in the neck. The blood study indicated a suspected diagnosis of infectious mononucleosis. However, the heterophil antibody test was negative. After a few days various other upper respiratory symptoms developed, such as sinus blocking and a bronchial cough, as well as conjunctivitis in one eye."

While I was intrigued by the description of this condition, I did not know that there was a recently recognized similar disease entity until this same friend called my attention to the article by Bell and co-workers.[1] This study from the U.S. Public Health Service, National Institutes of Health, National Microbiological Institute, reports the observation of over 300 cases of an acute respiratory illness, all with similar symptoms, occurring in the metropolitan Washington, D.C. area and in Leesburg, Virginia. The disease was characterized by fever, pharyngitis and conjunctivitis, present singly or in combination.

A newly discovered virus with specific antibody response was recovered from 30 of these patients. This virus has been classified as adenoidal-pharyngeal-conjunctival (APC) virus, type 3. Other viruses, types 1, 2, 4, 5 and 6, have been isolated from tonsil and adenoid tissue, but type 3, the causative agent of the disease reported, by the use of neutralization tests is considered to be type specific.

The epidemiologic evidence would seem to indicate that APC 3 virus was a causative agent of a definite disease. All the characteristics cannot be defined from this preliminary report. The disease occurred in a localized epidemic in a sporadic form in all age groups, but predominantly in children of both sexes. Infected human beings, not healthy carriers, were the source of the infection. Contaminated swimming pools may have transmitted the virus to some individuals.

The studies showed that the APC 3 virus invaded tissue exclusively during the acute illness and was rarely present before onset or after recovery. The fever often reached 104° F. and usually lasted from four to six days. The conjunctivitis was often monocular and lasted from one to three weeks.

How widespread the disease is cannot be stated at present, although there have been reports of similar cases in small groups since 1943.

The authors considered the differential diagnosis of leptospirosis, influenza, herpangina and various nonpurulent conjunctivides. There was no jaundice, and the clinical picture of severe

(Continued on page A-52)

*Emeritus Staff, Division of Clinical Pathology, Mayo Clinic; Director of Laboratories, Rochester State Hospital, Rochester, Minnesota.

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malaise and joint and muscle pain was absent. Agglutination-lysis tests with several *Leptospira* antigens were negative. The clinical details concerning some of these 80 cases were also published elsewhere.[2] However, the laboratory studies do not appear to have included attention to hematology or to serologic tests for heterophil antibodies.

Certainly there is no proof that the cases in Minnesota reported in my friend's letter were caused by the same virus. However, there is a striking similarity in the combination of symptoms. The cause of a similar outbreak could be verified only by careful studies in a virology laboratory and by the identification of type 3 adenoidal-pharyngeal-conjunctival virus. If further studies indicate that such widespread infection occurs, then the authors' suggestion that this disease be named pharyngealconjunctival fever is valid.

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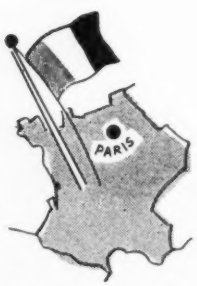


Psoriasis, a psychosomatic ailment—Several recent French publications discussing the various skin disorders support the theory of the psychogenic nature of psoriasis. However, physicians in general object to this further expansion of the psychosomatic etiology and the application of its therapeutic consequences. Bolgert, physician at the St. Louis Dermatological Hospital, strongly believes in the psychogenic nature of psoriasis. He has reported 200 observations in 104 men and 96 women examined by his coworker, Soulé, a psychiatrist. The questionnaire method was used primarily, supplemented by the Rorschach and Murray tests in children. Narcoanalysis was not employed.

Mental state—More than 50 per cent of the patients were psychasthenic, according to Janet's definition, with marked feelings of incompleteness in sensations and actions. These persons are meticulous, scrupulous individuals, victims of their own doubts and hesitations, which govern all their actions. They are without will power, are impressionable, and often superstitious. They often are accountants or bookkeepers. Ten per cent of the patients, two-thirds of them women, had anxiety and signs of obsession. The other third had no clear-cut mental abnormality.

Predisposing factors—These are the painful, affective symptoms which definitely appeared in one-half of the cases. In one-fifth of the cases, and playing a part in at least 68 per cent, the precipitating factor was shock, anxiety or frustration in the affective sphere; emotion; or, very rarely, material interests. This etiology is true in spite of the diminution of psoriasis cases during the war; psychasthenic persons improve during real danger.

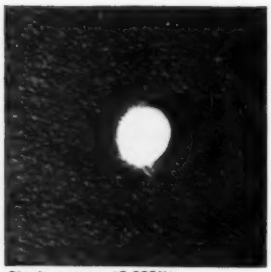
Heredity—This must be considered from two points of view, the heredity of dermatosis and the heredity of psychasthenia. The heredity of dermatosis shows an irregular dominance, according to Touraine, but it is related to other diseases, such as diabetes and chronic rheumatism, which could appear in the ancestors without psoriasis. The authors found 18 cases of psychasthenic heredity, in addition to seven cases of anxiety, in 37 patients whose family histories were studied.

Occurrence in children—There were 15 cases of psoriasis in children between the ages of 3

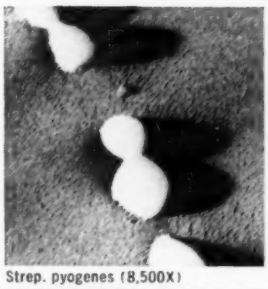
(Continued on page A-74)

The organisms commonly involved in

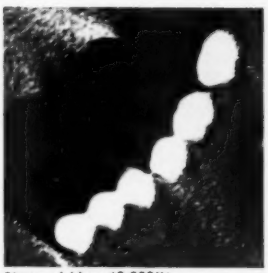
Bronchiectasis



Staph. aureus (9,000X)

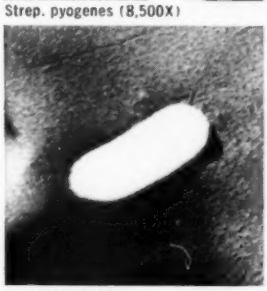


Strep. pyogenes (8,500X)



Strep. viridans (9,000X)

Strep. faecalis (10,000X)

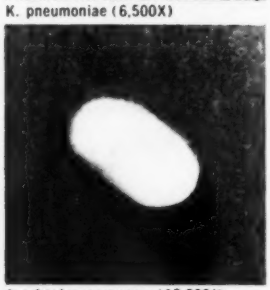


E. coli (8,000X)

K. pneumoniae (6,500X)

D. pneumoniae (10,000X)

H. influenzae (16,000X)



Aerobacter aerogenes (12,500X)

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and 14. The authors found five obsessions, two anxiety neuroses and seven normal personalities. In 12 cases the precipitating factor was a disturbance in family life (quarrel between parents, divorce, etc.). The hereditary factors, both dermatologic and psychasthenic, were more apparent in children.

Minor nervous symptoms—Frank pruritus is rare, but moderate itching which does not exist until the patient thinks of it could be seen in 75 per cent of cases. Occasionally there was a burning sensation, rather than itching, which was increased by contact with clothing. This was first observed in 1888 by Bourdillon. There may be sleeplessness at the time of eruption. Small changes could also be noticed in encephalographic tracings.

Some precipitating value is attributed to infections, furunculosis and tuberculosis, but it is questionable whether it is the mental repercussion rather than the actual infection itself that is the important factor.

Dermatologic aspects—These vary according to the nature of the mental trauma. Sudden, brutal mental shock results in the generalized type of psoriasis guttata after an incubation period of from one to six days. Mental difficulty which is the result of long meditation and intellectual elaboration gives rise to polymorphic eruptions, with plaques and spotty efflorescence, after an incubation period of several weeks. When the environment responsible is of long duration, without sudden emotional shock, onset of psoriasis is slow.

The site of eruption may correspond with the area causing the most worry to the patient, i.e., perineal eruption in worries of sexual origin such as impotence, on the limbs when worries refer to work, and on the scalp and ears in sentimental moods.

Treatment—This is of little benefit, unfortunately. The disappearance of the precipitating mental cause is the most favorable sign. Among the medicaments for the sympathetic nervous system, atropine in repeated small doses and eserine are successful. Electroshock gives only transient good results, and the ganglioplegics are of no value. The mental element acts through a substance which is perhaps secreted in the central nervous system or under central nervous control and which we are unable to neutralize (Semaine d. hôp. Paris, May 1955, pp. 252-265).

(Continued on page A-76)

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1. Reader, T. J. Jr.: at Mtg. Med. Assoc. St. Alabama, Mobile, 1954.
2. Jessup, R., Murray, R. J. and Rossi, A.: Amer. Pract. & Dig. of Treatment, 5:792, 1954.

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GENEVA

World Health Organization—The fifth regular session of the WHO Regional Committee for Europe, held in Vienna in September, was attended by delegates from 21 countries. Dr. A. Khaum, of Austria, was elected chairman.

The Committee outlined a general guide for WHO policy in Europe during the period 1957 to 1960. Particular stress was given to activities in which several or all countries in the region will take part. The principal aims will be to study common health problems, to exchange knowledge, and to develop training facilities for medical and health personnel. Emphasis will be given to further study of chronic diseases of public health importance in Europe, such as diabetes, cancer, rheumatism and the cardiovascular diseases. Accident prevention will also receive more attention.

The Committee endorsed a five week training course in protection against radiation, to be held in November and December 1955 at the Karolinska Hospital in Stockholm. The course is intended for physicists concerned with problems of health and subjects to be included will cover laboratory design, protection of factory workers, and disposal of atomic wastes. The course is a development of the recent Geneva Conference on the Peaceful Uses of Atomic Energy and will be the first international course of its kind.

Two other activities were added to the 1955 program: a meeting of specialists in tuberculosis control to be held in Luxembourg, and a survey of drinking patterns in Europe, to be undertaken by the International Institute for Research on Problems of Alcohol.

A meeting to study the prevention of accidents in childhood, and a seminar on child guidance were added to the 1956 program.

Following the resolution taken by the World Health Assembly this year that a serious attempt should be made to eradicate malaria in all parts of the world, the Regional Committee, after reviewing the situation in Europe, agreed that strong intergovernment cooperation will be necessary if the disease is to be markedly reduced. The Yugoslavian delegation, in particular, stressed the need for such cooperation and for a free ex-

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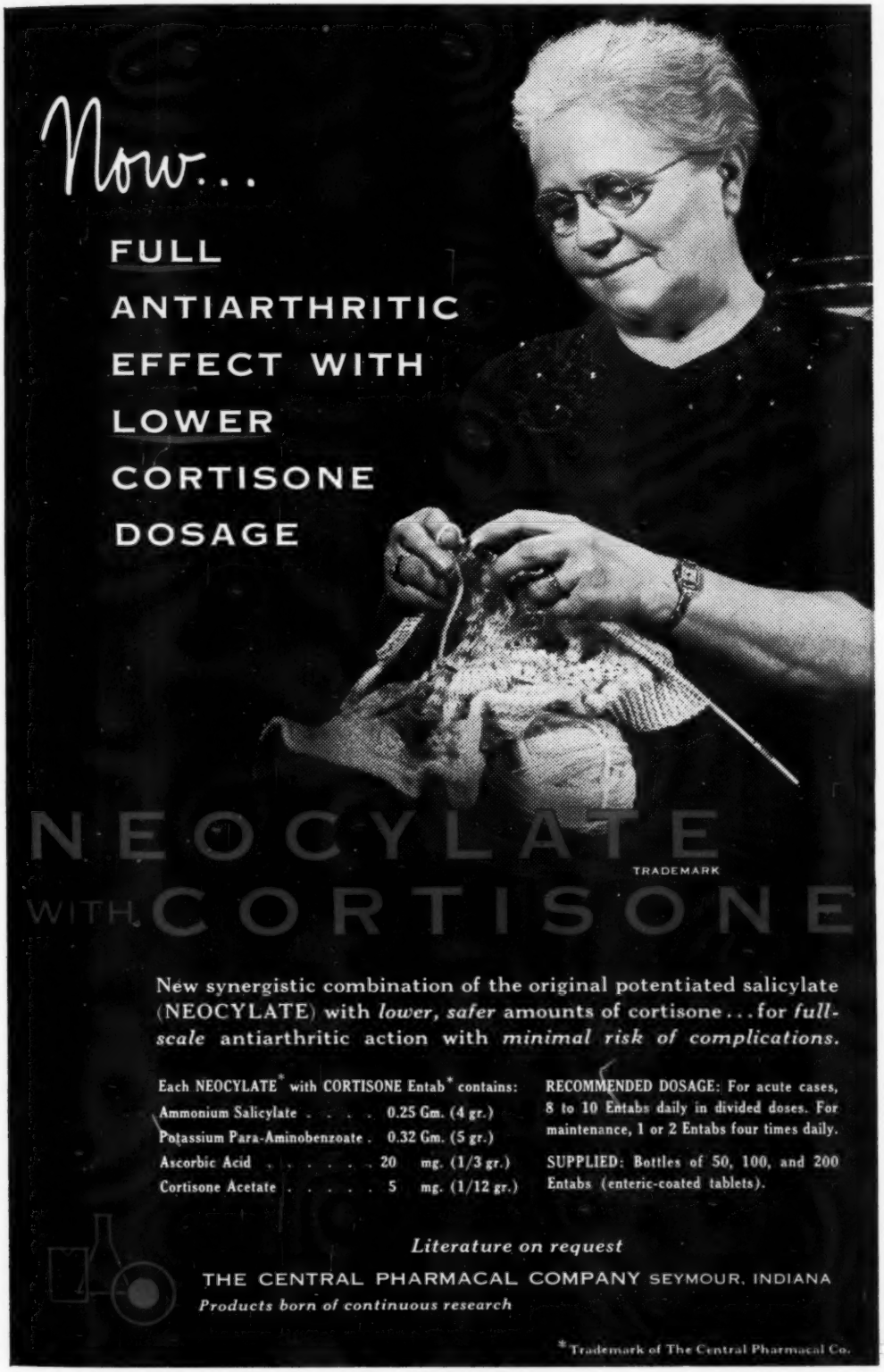

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change of information among countries of southeastern Europe. Without such cooperation malaria eradication is not practical. At present, there are about 800 cases of malaria every year in Yugoslavia, and the government is prepared to make an all-out campaign. The delegate from Greece, in describing the situation in his country, said that in the 1930s 15 to 30 per cent of the population was afflicted with malaria and that some 20 to 40 million working days were lost every year as a result. With international assistance, very effective campaigns were started in 1945, and by 1951 spraying with insecticides could be halted in two districts. Since that time the area where spraying was no longer necessary has been gradually increased, which has meant a considerable saving of insecticide and labor. One variety of mosquito, however, developed some resistance to DDT®, and since 1954 spraying has had to be resumed.

The informal technical discussion on changes in health services necessitated by the aging of populations led to a lively exchange of views. Some figures supplied indicate the extent of the problem. In Sweden, a country with almost 7,000,000 inhabitants, about 10 per cent of the population is above the official retiring age, that is, 67 years old, and this percentage is gradually increasing. In Great Britain, most house calls made by general practitioners are for persons over 65 years of age. They make between three and four visits to patients over 65 as compared with one visit to patients below that age. For the district nurse the difference is even greater. They estimate eight calls to patients over 65 as compared with one to patients under 65.

Keynote of the discussion was that mere preservative care of the aged is no longer sufficient. When ill, they should be treated with the same energy and skill as any other patients, and no effort should be spared to restore them to mobility and, as far as possible, to health. Being admitted to a hospital is very often a shock for the aged patient, and for this reason, as well as for practical financial reasons, old people should be treated at home whenever possible.

The Committee will meet in 1956 in Rabat, Morocco, and the subject of the technical discussion will be the prevention of accidents in the home. The 1957 meeting will be held in the new regional headquarters in Copenhagen, the date to be determined by the length of time necessary for the Danish government to complete the building to house the regional office for Europe.

X-ray Diagnosis of Cancer of the Lung

LEO G. RIGLER*

University of Minnesota Medical School, Minneapolis

LEO G. RIGLER

THE increased frequency of carcinoma of the lung represents one of the most pressing problems in modern medical practice. It is certainly clear that in males, at least, there is a striking and steady rise in the incidence of bronchogenic carcinoma. Statisticians have predicted that if the rate of increase exhibited during the past two decades should continue for the next two decades, we would be faced with a real national disaster—at least if the decimation of the male population could be considered a disaster.

We hear a good deal about the cause of this increase, and there is much speculation. All of you, I am sure, are reading about cigarettes, long and short, filtered and unfiltered, about pollution of the atmosphere, and many theories as to why this increase has occurred.

While we are trying to find the cause of this increase, while we are exerting every effort toward prevention, something must be done to salvage those who are now affected and the many who will be affected in the future by this almost uniformly fatal disease.

There is a curative procedure: surgery—pneumonectomy or lobectomy. The chances for its success depend in large part on the early detection and rapid identification of this disease.

For some years we have been investigating what might be called the past x-ray history of individuals known to have carcinoma of the lung. Examination of chest films made fortuitously for other reasons or during a chest survey, without any suspicion of carcinoma, in these cases discovered in other hospitals and other institutions, has indicated to us that carcinoma of the lung is a relatively indolent tumor more frequently than not—that it may go on, in fact, for a number of years. In our

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Presented before the thirty-ninth annual Assembly of the Interstate Postgraduate Medical Association at Minneapolis.

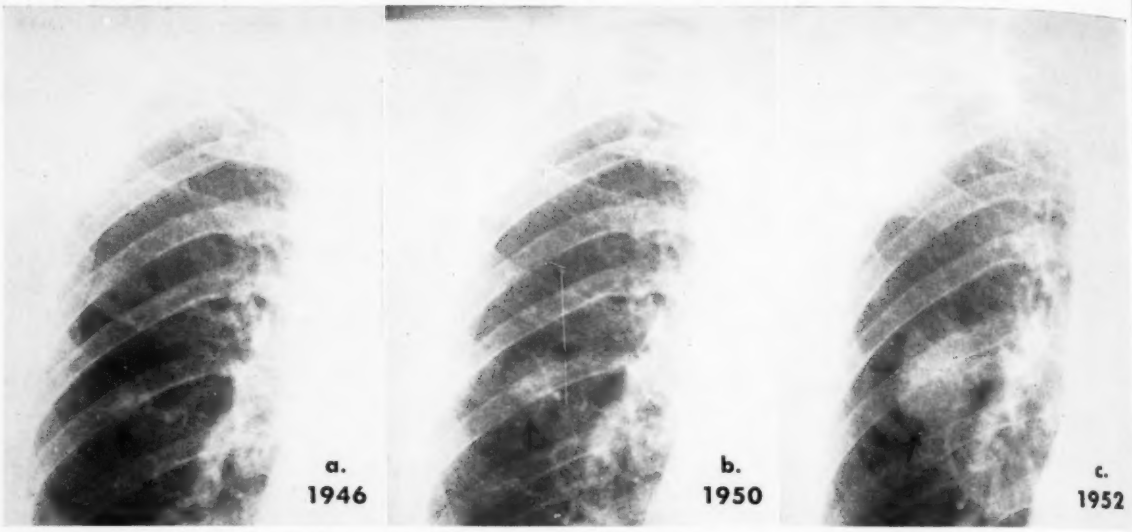


FIGURE 1. Development of adenocarcinoma from a minimal peripheral lesion to a major lesion in a bronchus.
(Courtesy of Dr. G. A. Hedberg.)

a. Routine roentgenogram, 1946. Small nodule overlying rib (arrow), overlooked at that time but clearly visible in retrospect.

b. Routine roentgenogram, 1950. The shadow has increased considerably in size (arrow).

c. Routine roentgenogram, 1952. The shadow not only has increased in size (arrow) but is extending medially. The patient was still asymptomatic.

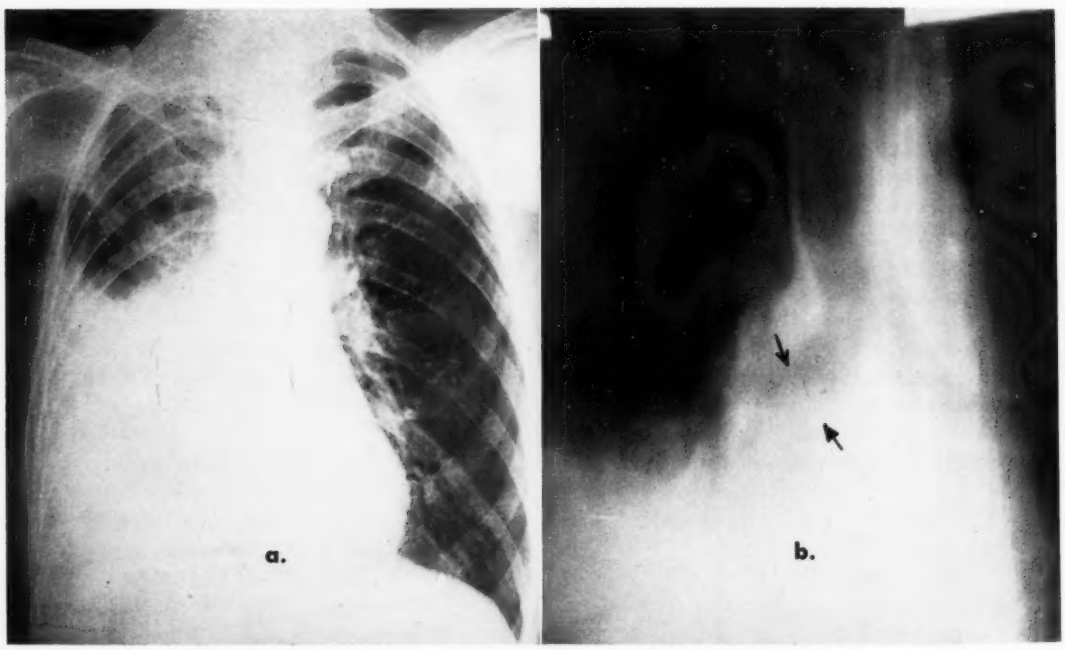


FIGURE 2 (same case as figure 1). Roentgenograms of chest taken in 1953, six months after onset of symptoms and seven years after first roentgenologic evidence of a lesion.

a. Routine film shows atelectasis of right lung and small amount of fluid in pleural cavity.

b. Body section roentgenogram (planigram) showing mass in right lower lobe bronchus (arrows). Tumor has obviously extended into this bronchus from the periphery.

series, an average of well over two years elapse from the time the first evidences are seen on the roentgenogram before it is positively diagnosed or anything is done about it. We have also found that carcinoma of the lung exhibits signs in the x-ray film of the chest on an average of nine months or longer before the patient is aware of first symptoms. Further, repeated roentgenologic studies usually reveal evidence of the disease process in its very earliest, or at least we might say smallest, stages.

The following case illustrates the type of material we have been seeing. I am indebted for some of these films to Dr. Hedberg of Nopeming, Minnesota. The patient was a woman who lived in northern Minnesota. She had a carcinoma of the breast. Because of this, chest films were made in an effort to determine whether or not metastasis had occurred. We had access to films made in 1944 and 1945, at which time nothing abnormal was seen. Then, in 1946, there appeared for the first time a tiny nodule or density (figure 1a) about 5 mm. in diameter. Nothing was done about it; it was not observed at the time, and so the x-ray was considered negative. From 1946 to 1950 there were no x-ray examinations. In 1950, a larger, much more apparent shadow was seen in exactly the same place (figure 1b). By 1951, the nodule had increased in size; a film taken in 1952 showed a further increase (figure 1c). In 1952 she was observed at a clinic and advised to have an operation to remove the lesion, but she refused.

In 1953, seven years after the first visible roentgenologic evidence of a lesion, she came to us with symptoms of three or four months' duration—characteristic symptoms of cough, hemoptysis, pain and loss of weight. At this time she had an extensive atelectasis of the right lung (figure 2a). With body section roentgenography, blurring out the other structures, one can see (figure 2b) that the trachea and the right bronchus and the tumor itself had advanced from the periphery centrally to form a large obstructive mass in the bronchus, which, of course, as Dr. Jackson has shown, could be demonstrated easily by means of the bronchoscope. She was operated on. The tumor was an adenocarcinoma.

It is evident from cases of this type (and we have seen a great many of them) that a small density produced in the periphery of the lung by a tumor arising in a small branch bronchus may be detected at a very early stage. One may well ask, then, how small a lesion can one see in a roentgenogram? We have had some experience with this. If a patient has a primary tumor elsewhere in the body, one often makes films of the chest at repeated intervals, say at six month intervals, in the hope of discovering a metastasis at the earliest time when it will appear, and we have been able to show metastases as small as 3 mm. or even less in size.

Perhaps the smallest primary carcinoma of the lung that I have ever seen was in a roentgenogram of the chest sent to me by Dr. Samuel Richman. The patient entered a Veterans Hospital because of some complaint which had nothing to do with his lung, and routine examination of the chest, such as is usually done in a Veterans Hospital, disclosed a rounded, dense shadow measuring 3 cm. in diameter (figure 3a). The shadow itself did not necessarily mean it was a carcinoma, but at any rate a strong suspicion was aroused.

Looking back into his record, it was found that two and a half years previously he had been in the same hospital for another condition, also not related to his lung, and a chest film made at that time had been called negative. But in exactly the same area there is seen, in retrospect, a small lesion only a few millimeters in diameter, which undoubtedly represented the first evidences of this tumor (figure 3b).

Obviously, we do not find such lesions frequently. It really should not be difficult to detect such peripheral nodular lesions, since they stand out very strikingly in contrast with the surrounding brilliantly illuminated air-filled lung. Yet we frequently fail to observe even larger lesions or we fail to give sufficient credence to them.

The real problems in regard to such peripheral lesions lie in their identification, the determination that they are tumors, and the

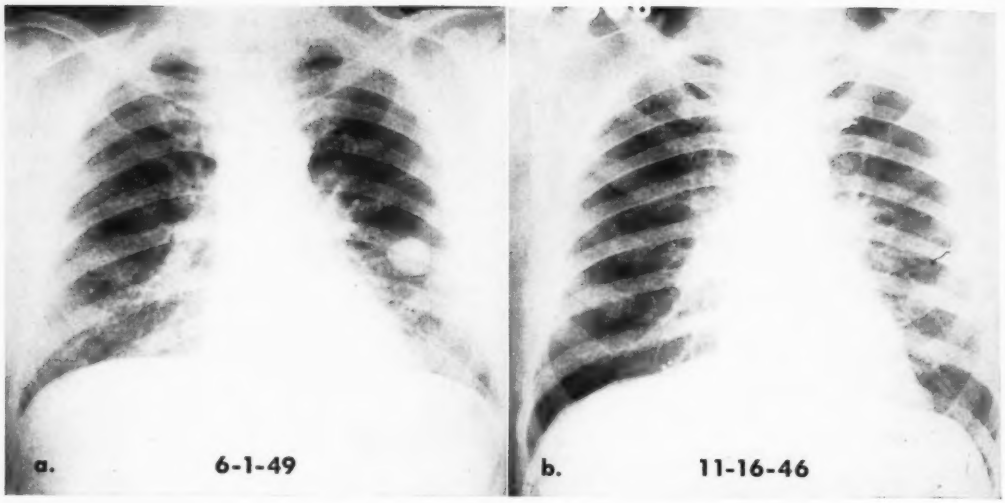


FIGURE 3. Squamous cell carcinoma of lung discovered on routine examination of a patient without pulmonary symptoms. (Courtesy of Dr. Samuel Richman.)

a. Routine roentgenogram taken June 1, 1949 showing sharply defined, rounded nodule in left lung. From this finding alone, the diagnosis would not be definite.

b. Routine roentgenogram made November 13, 1946, two and a half years before, shows tiny nodule in same area (arrow), indicating growth of lesion over this period.

pressure to consider them as serious matters.

The numerous chest surveys carried out in this country have not been strikingly successful in finding early carcinomas of the lung. One reason for this lack of success is that we have done them hastily and without close attention to such minor changes as I have mentioned. Let me illustrate with another case.

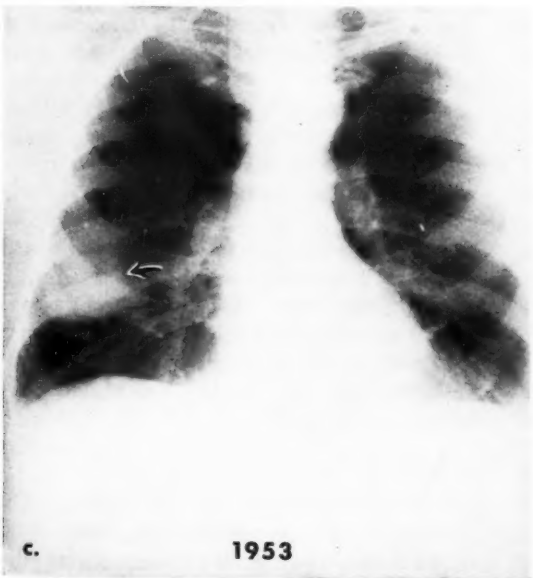
The patient in point, a doctor, is in charge of a section in a large hospital, where the staff and employees have chest films made regularly every year. The film made in 1951 (figure 4a) was apparently entirely normal so far as we can determine, even in retrospect. About a year and a quarter later another routine film was also called normal, but on closer examination, at least in retrospect, there is found a distinct small nodular mass over one rib which was overlooked (figure 4b). A year later, the patient still did not have symptoms, but the roentgenogram revealed a mass which had grown so large that it was perfectly obvious (figure 4c). Many other studies were made at this time, and the diagnosis of carcinoma was made on the basis of the rapid increase in size, and the cavity and notch found in the planigram (figure 4d). He was operated on, and the mass proved to be a squamous cell carcinoma. He should have been operated on a year earlier; his chances for survival would have been infinitely greater when the mass was only 1 cm. in diameter.

Can we, however, detect the deeper-seated lesion, the one which is not so well demarcated in the periphery? Here, too, we believe it is possible to demonstrate lesions at a very early stage, lesions which exhibit themselves as a disease process and require other types of identification. The problem is much more difficult, since most of these deep-seated lesions, those in the center of the lung which arise in the major bronchi, exhibit themselves by increasing the size of the hilus. We know that anatomic variations in the hilus are of such an order that it is difficult to distinguish change when the enlargement is minor. Further, inflammatory disease tends to produce some changes in the hilar shadows as well.

FIGURE 4. Squamous cell carcinoma of the lung, showing development.
(Courtesy of Dr. Samuel Richman.)

a. Routine roentgenogram, asymptomatic individual. Entirely negative.

b. Routine roentgenogram taken one year later. Small nodule (arrow) was not noted at that time.



c. Routine roentgenogram one year later (patient still asymptomatic) shows fairly large mass in same area.

d. Body section roentgenogram (planigram) showing cavity in the mass (arrow) and notch on lower border (arrow), both strongly indicative of carcinomatous nature of the process.

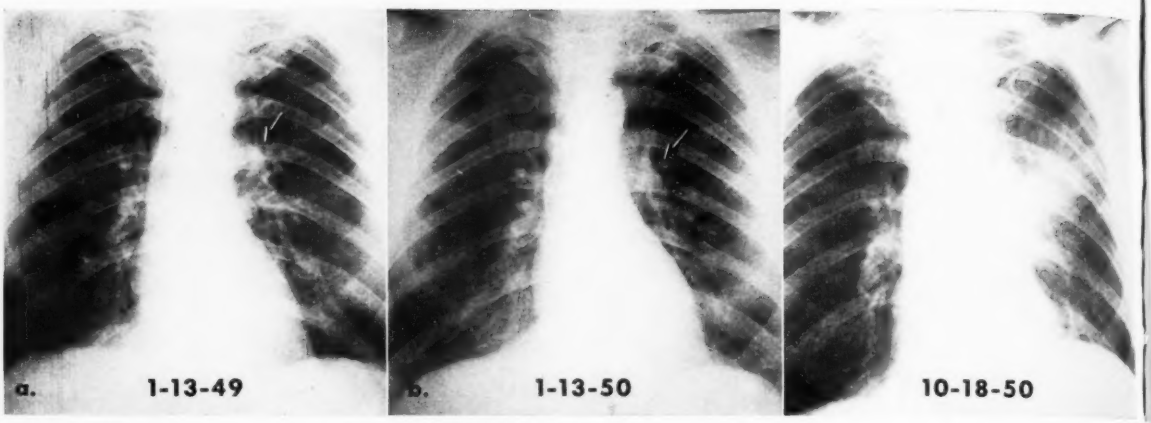


FIGURE 5. Squamous cell carcinoma of the lung exhibiting itself by mass in hilus.

a. Routine roentgenogram, asymptomatic individual. Normal left hilus (arrow).

b. Routine roentgenogram taken one year later (patient still asymptomatic), showing enlargement of hilus which was not observed at that time.

c. Roentgenogram of chest made four months after development of symptoms and nine months after the film shown in figure 5b, showing characteristic atelectasis of left upper lobe and mass in left hilus. Note the elevated left diaphragm.

Nevertheless, I think if we paid close attention to these changes, particularly when we have earlier films for comparison, we could make this diagnosis, or at least suspect it, much earlier than we have been doing in the past.

A case which illustrates how easy it is to overlook the shadow of an enlarged hilus was observed in our own clinic. The patient came to the Cancer Detection Clinic without any symptoms whatever, perfectly well. A routine film of the chest was made and the hilar shadows on the two sides were equal and entirely normal (figure 5a). The patient was seen again in exactly a year, still entirely well, apparently. However, the hilar shadow on the left side, when compared with the opposite side, showed a very striking change (figure 5b), which was overlooked. If the second film had been compared with that made a year earlier, this change would not have been overlooked. Comparing the normal with the abnormal side should arouse our suspicion at once, and it is important that suspicion be aroused, because in this type of lesion bronchoscopy or examination of the sputum usually will demonstrate the nature of the process immediately. Suspicion was not aroused in this case, and six months elapsed after this before he had any symptoms whatever, and about three or four more months elapsed (that is, about nine months from the last film) before he was examined and a large mass in the hilus, atelectasis and all the findings which go with a well-advanced tumor were noted (figure 5c).

There is no doubt, of course, that a patient may have symptoms, bronchoscopic evidences of carcinoma, or tumor cells in the sputum and yet the x-ray findings appear entirely negative. But of about 400 cases which we studied this was the situation in only two, and I suspect it is a very rare occurrence. Actually, in almost all our cases, the x-ray findings appeared well before the onset of symptoms. As I said, in only two were symptoms present without obvious or at least some evidences of disease in the lung.

Early Signs

What are the early signs which may help us to detect the disease process, later to be identified as carcinoma of the lung, in the roentgenogram in a stage when it seems reasonable that operability would be greatly im-

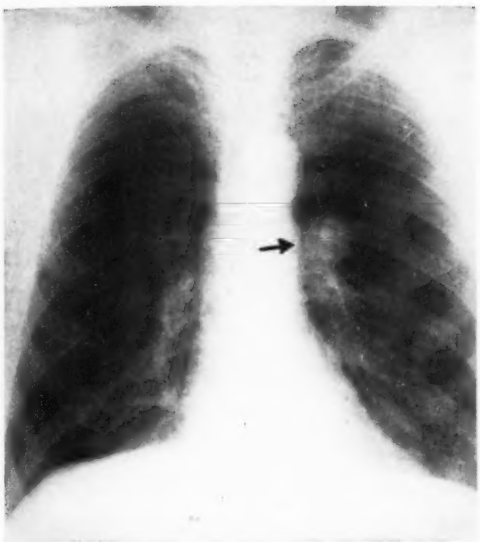


FIGURE 6. Carcinoma of the left lower lobe of the lung. Routine roentgenogram of the chest made 18 months before obvious symptoms and signs appeared, showing mass in left hilus (arrow) which was overlooked. This proved to be a bronchogenic carcinoma which was inoperable when the patient presented himself because of symptoms 18 months after this roentgenogram was taken.

proved over its later status? I have already mentioned the peripheral density usually appearing as a solitary shadow. Second is the unilateral enlargement of the hilus which I have described.

A good example is illustrated by the patient who comes to us with a story of cough, hemoptysis and loss of weight—all the classic signs that we associate with carcinoma of the lung. We find that he has extensive atelectasis of the left lower lobe and a very large mass in the hilus, and the x-ray picture is quite typical of carcinoma. He has had symptoms for about nine months. But when we look back into his previous history we find that 18 months previously he had a film made in a hospital; there was no clinical reason for it except that it was routine. As a matter of fact it was a miniature film, a photofluorogram, and he was told at the time (we looked up the record) that it was negative. Yet when we examine the film we find that the left hilus is very distinctly enlarged compared with the opposite side (figure 6). Attention should have been called to this at the time and further investigation undertaken.

One other sign that we have found in the early stage of the disease, a sign which perhaps is overlooked even more frequently than the two already mentioned, is a lobar or unilateral or segmental emphysema. This occurs in the early stages of a partial bronchial obstruction in which the tumor is partially closing the bronchus without completely closing it, so that air can get into the lobe but cannot get out. As an illustration, let me describe a patient going through one of these city-wide surveys. A miniature film, a photofluorogram, is made and called negative (figure 7a), but careful study reveals that the left lower lobe is distinctly more radiable than the right lower lobe, more radiable than any of the other lobes, in fact, and that the left hilus is a little more irregular, although not strikingly so. This is the finding of obstructive emphysema of the left lower lobe.

When the same patient is seen some two years later, the left hilus has greatly increased in size, there is atelectasis of the same lobe, the emphysema has disappeared, and we have the usual and characteristic picture of fairly well-advanced carcinoma (figure 7b).

Another case illustrating the importance of emphysema as a sign was that of a man admitted to a hospital because of an abdominal condition. A routine film of the chest was made and considered to be negative. Examination, however, reveals clearly an emphysema of the left upper lobe and a moderate enlargement of the left hilus (figure 8a). He had no pulmonary symptoms. Three months later he developed what was thought to be a pneumonia, which did not resolve. We saw him two months later, when the emphysema of the left upper lobe had been converted into atelectasis and the mass in the left hilus was greatly increased (figure 8b). He was operated on at that time. A squamous cell carcinoma of the left upper lobe bronchus was found and a pneumonectomy done. The patient is still alive after more than 10 years. Again, the lesion was present before he had

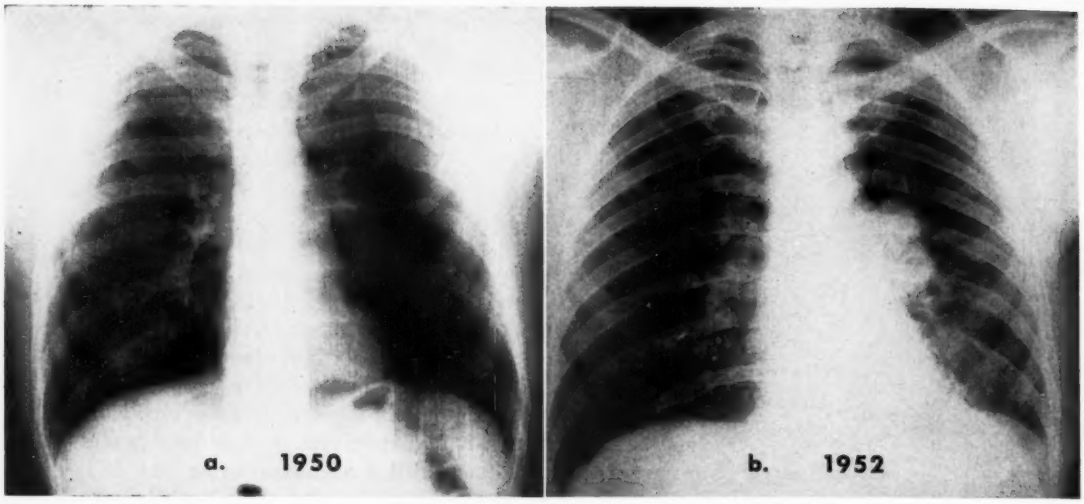


FIGURE 7. Emphysema as an early sign of bronchogenic carcinoma.

a. Photofluorogram made in 1950, considered to be negative but, in retrospect, clearly showing emphysema of the left lower lobe and moderate enlargement of the left hilus. Patient was asymptomatic at that time.

b. Symptoms of carcinoma have appeared, and roentgenogram of chest shows markedly enlarged hilus on the left side, with atelectasis now in the lower lobe supervening on the emphysema which was present previously.

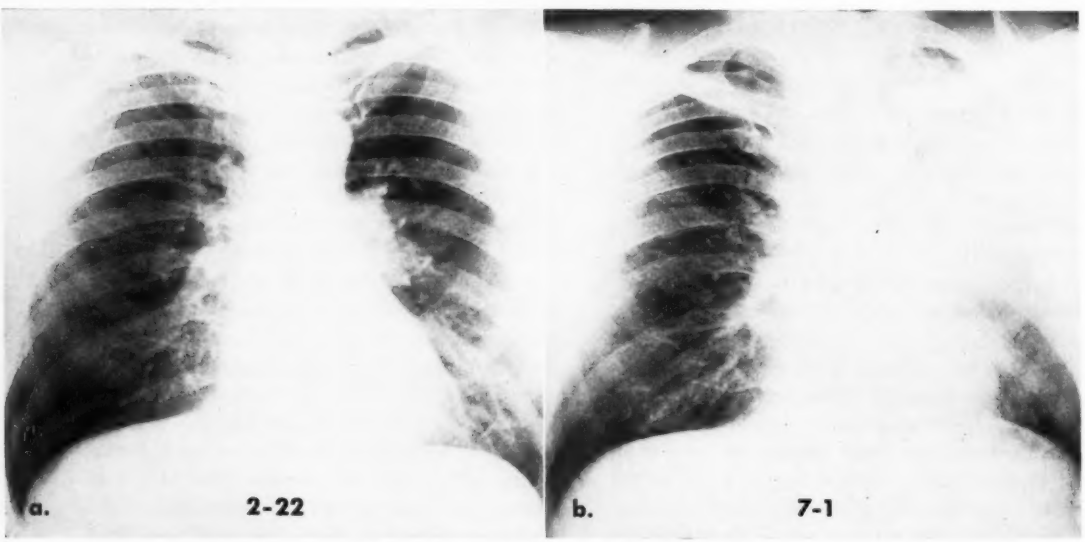


FIGURE 8. Emphysema as an early sign of carcinoma of the lung.

a. Routine roentgenogram (asymptomatic individual) considered negative but actually showing enlarged left hilus and moderate emphysema of left upper lobe.

b. Same patient, four months later. The emphysema of the left upper lobe has now changed to atelectasis and the mediastinal mass is greatly increased in size. The patient was thought to have unresolved pneumonia clinically, but the roentgenologic findings were characteristic. Squamous cell carcinoma of the left upper bronchus was found at operation.

(Reproduced courtesy of *Radiology*.)

any symptoms, and the obvious evidences of it were present in the roentgenogram clearly before that time.

These are signs (there are others which I would not want to go into any further) which give us some idea that it is possible to detect a lesion of the lung at a very early stage.

Diagnostic Signs

When we find evidence of a disease process in the lung, we have the problem of determining its nature. This, of course, is infinitely more difficult. It is relatively easy to detect an abnormal process in the lung in the roentgenogram. However, carcinoma of the lung is particularly difficult to identify as to its exact nature, because it is without doubt the great simulator of all other types of disease to which the lung is heir. This pathologic state may produce a growing mass in the lung, necrosis and abscess formation, secondary inflammatory reaction, perilymphatic and perivascular infiltrative processes, and partial or complete obstruction of the bronchus, segmental or otherwise, with all the pulmonary sequelae which follow it. Such a process obviously may simulate almost any lesion which affects the lung. With the increasing use of x-ray examination in apparently normal individuals, the problem of differential diagnosis has become extremely pressing. The finding of an abnormal shadow in a roentgenogram of the lungs of an apparently healthy individual puts a very grave responsibility on the physician in charge.

There are many methods whereby a definitive, unequivocal diagnosis of carcinoma of the lung may be established. The most important of these, of course, is the microscopic examination of tissue removed either through the bronchoscope, by percutaneous biopsy, or as the result of open thoracotomy. Direct visualization of the tumor through the bronchoscope in itself is often an effective and fairly definitive means of diagnosis. The demonstration of carcinomatous cells in the sputum or in material obtained by bronchial aspiration is another excellent method for positive identification. But with all these methods there are still a substantial number of patients with an abnormal process in the lung in whom none of these methods are really effective. In some instances they are ineffective because of our inability or reluctance to use them. For example, many people object to percutaneous lung biopsy; they feel it is very dangerous. Despite the relatively innocuous character of exploratory thoracotomy, there are many cogent reasons for not wanting to open the chest in every case in which one observes an abnormal shadow in the roentgenogram.

For these reasons, we have tried to determine whether by the simple means of roentgenologic examination a more definitive diagnosis could be made than has usually been thought possible by this means. We know there are distinct limitations in the roentgenologic determination of the exact nature of a disease process. People say that this is just a shadow and ask, how can you tell what the shadow is? But there are distinctive roentgenologic signs which seem so characteristic of malignant tumors that they carry weight approaching, although not the same as, that of the finding of actual tumor cells. It should be emphasized that all diagnoses, even those made at the autopsy table, are probabilities only. Errors occur in all of them. The essential difference between the lung biopsy and the positive roentgenologic identification of a tumor is that the former is more accurate. The difference, therefore, is one of degree, not of kind, and the next case illustrates this point.

This patient came to his physician with what appeared to be pneumonia. He was treated for two or three weeks but did not quite get well. His physician began to suspect something much more serious, perhaps carcinoma, and sent the patient to us with that thought in mind. The patient had a moderate fever, a little leukopenia, and very little else to go on. He had had one bout of hemoptysis during his "acute pneumonia," about a month previously. A film of the chest (figure 9a) showed a broad band of consolidation filling part of the right upper lobe, with one feature which is very striking in our experience, namely, a bulging margin, which very often connotes the fact that this has something to do with tumor. With this thought in mind, fur-

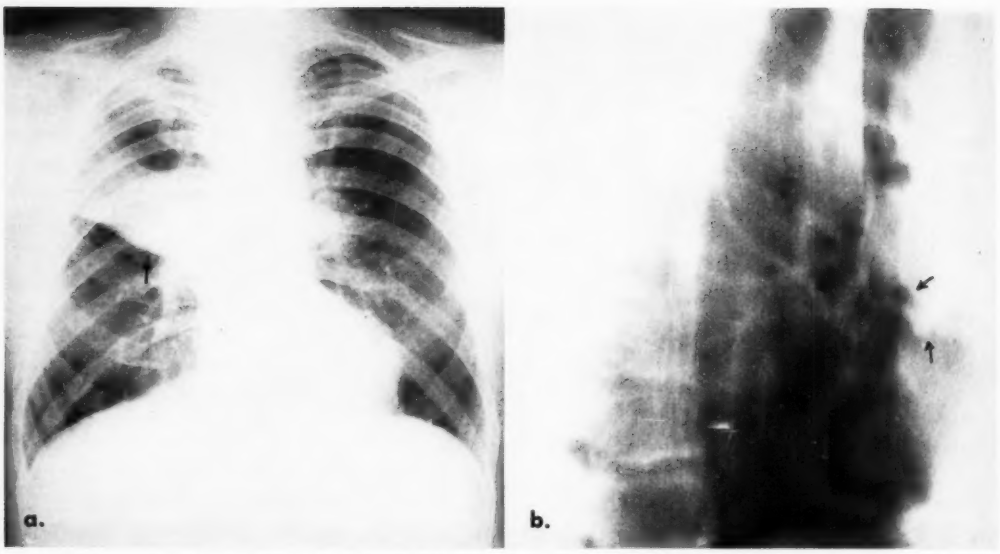


FIGURE 9. Squamous cell carcinoma of the lung. This case illustrates characteristic findings and the importance of body section roentgenography (planigraphy).

a. Consolidation in right upper lobe following what appeared to be pneumonia. Note bulging inferior margin medially (arrow), strongly suggestive of carcinoma.

b. Body section roentgenogram, lateral view, showing obstruction of axillary branch of upper lobe bronchus (arrow) with small mass alongside (arrow), indicating carcinomatous nature of lesion.

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ther studies were undertaken by means of body section roentgenography. We were able, by means of planigraphy in the lateral position, to demonstrate that the anterior branch of the right upper lobe bronchus ended abruptly just beyond its take-off (figure 9b). A stenosis of the bronchus in association with pneumonia is quite unusual—quite rare, in fact—and so we felt this proved almost beyond a doubt that this patient had a carcinoma of the anterior branch of the right upper lobe bronchus.

He was operated on by Dr. Varco. At operation a dense, infiltrative upper lobe was found with some nodular masses within it. Three or four biopsies were done at the operating table. Frozen sections were made from these biopsies (a frozen section, of course, is a very unsatisfactory method for microscopic study), but all of them came back with a diagnosis of inflammatory tissue. Despite this, Dr. Varco, with a good deal of courage, because of his own surgical findings and the previous x-ray findings, proceeded to do a definitive operation, that is, a pneumonectomy. Within about four or five days, as a result of study of paraffin sections, it was possible to make a diagnosis of squamous cell carcinoma of the lung which was unequivocal.

I cite that example not to indicate that x-ray examination is usually or even frequently more accurate than the histologic examination, but rather to point out that under unfavorable conditions the histologic examination may be in error and certain distinctive signs such as the association of a dense shadow with a mass, together with an obstructive bronchus, are so definitive, so indicative of carcinoma, that they justify an exploratory and definitive operation.

There are a few more of these signs which we think are extremely important. For example, given a man of middle age, without symptoms, in whose roentgenogram one finds a

small, rounded, sharply defined peripheral nodule in the lung, the question of its etiology is extremely difficult. But, as is so often the case today, if you have an earlier film and find that there is no such shadow in that film—that he had a perfectly clear film before—and now, a year later, suddenly at this age a nodule develops in his lung, the probabilities that this is a carcinoma of the lung are exceedingly great and one should so assume, at least until proved otherwise. Certainly one would be justified in doing an exploratory thoracotomy with removal of the nodule.

If you have the good fortune to be able to get enough films to observe a lesion of this kind growing under your very eyes, then, of course, the diagnosis is even more certain.

One of our interesting cases was that of a woman who had gastrointestinal symptoms but no pulmonary symptoms whatever. We saw her first in 1953. A small, rather faint segmental density was noted in the left upper lobe (figure 10c). She had been going from one clinic to another with these gastrointestinal symptoms—having gastrointestinal studies and x-ray examinations of the colon and gallbladder, all proving negative. Here and there someone made a film of the chest just as a matter of routine. So when we went back into her history about 13 months we found a film which had been called negative but which, in retrospect, at least, showed certainly a nodule in exactly the same area and having somewhat the same characteristics although it was but one-fourth the size (figure 10b). When we went back about a year and a half, we found that she had had another film made at another place which showed the same nodule, except much smaller (figure 10a). If you follow such films along, therefore, it becomes evident that the lesion is growing under your very eyes and a diagnosis of carcinoma can be made with certainty.

In this case we also made a planigram. This revealed what we think is an extremely characteristic sign of carcinoma, that is, a little notch in the margin of the shadow, as shown in another case (figure 4d). Then we were quite certain that this was carcinoma, which it proved to be. Dr. Kremen did a lobectomy

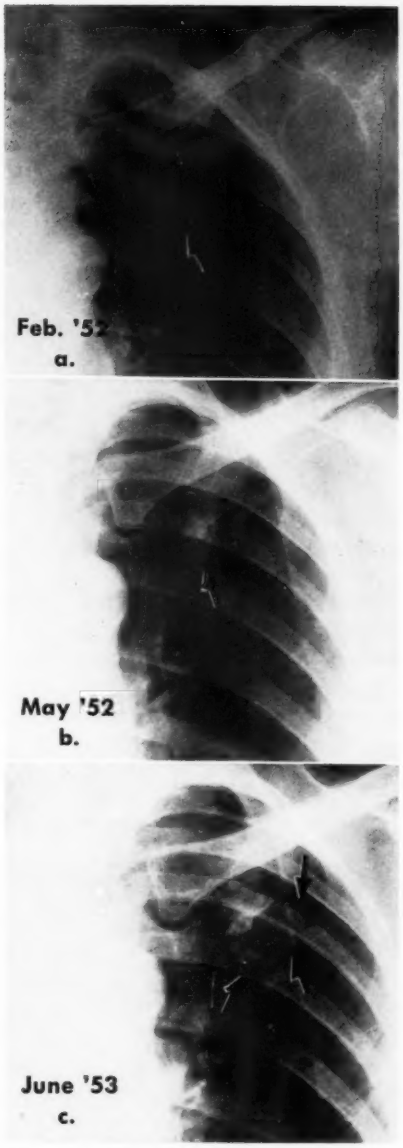

FIGURE 10. Alveolar cell (bronchiolar) carcinoma of the left upper lobe developing from a small lesion.

a. Routine roentgenogram, February 1952, asymptomatic individual. A tiny lesion in the left subclavicular region (arrow) was overlooked at the time this film was made.

b. Routine roentgenogram taken in May 1952, patient asymptomatic. The small density seen in the earlier film has increased appreciably in size (arrow), but it was overlooked.

c. Routine roentgenogram, June 1953, patient still asymptomatic. Large, fairly obvious shadow in the left subclavicular region (arrows) indicates the growth of the lesion—growth sufficient to indicate the carcinomatous nature of the process.

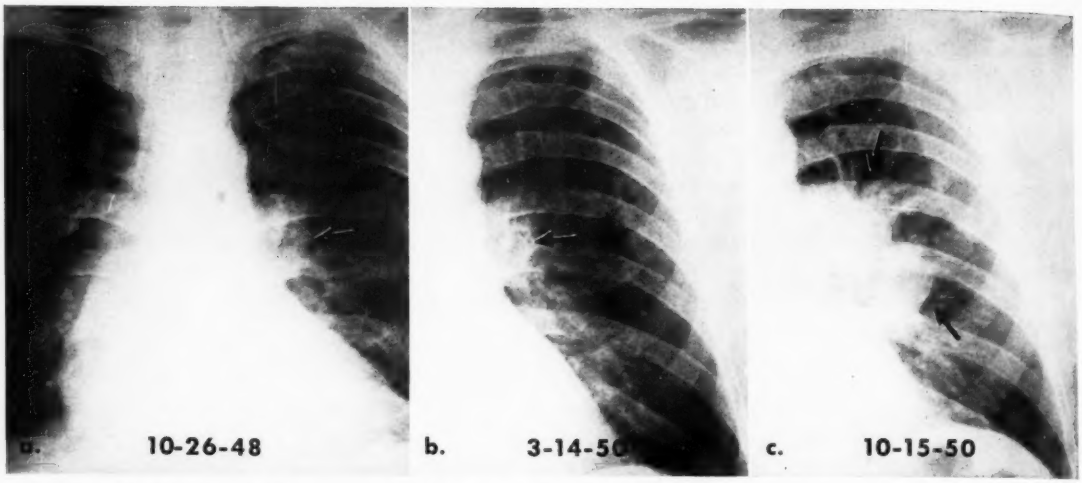

FIGURE 11. Squamous cell carcinoma of the left lung, showing development of hilar shadow and demonstration of bronchial occlusion.

a. Routine chest roentgenogram of patient with cardiac symptoms but no pulmonary complaints. Enlarged left hilus (arrow) was overlooked.

b. Further enlargement of the hilus (arrow) is apparent in film made 17 months later. Patient still asymptomatic.

c. Nine months later, a film shows marked lobulated, enlarged mass (arrows). Patient now has symptoms.

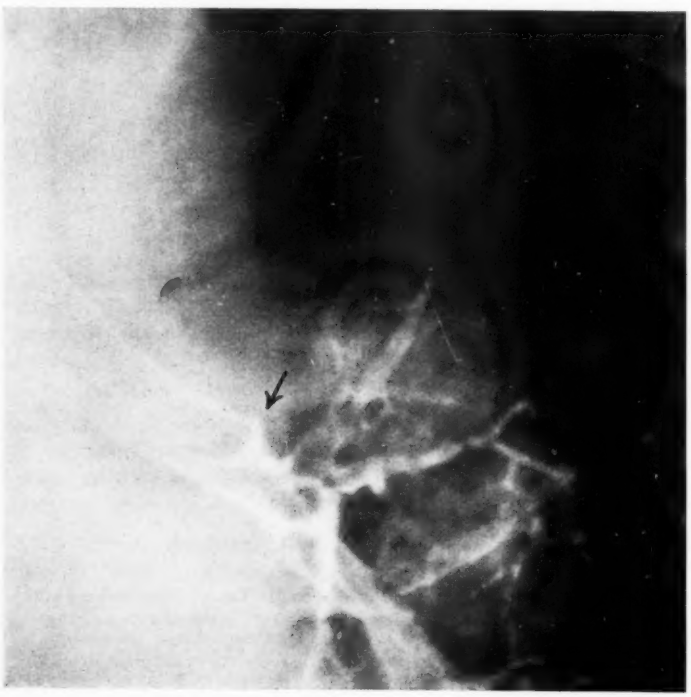

FIGURE 12 (same case as figure 11). Bronchogram showing obstruction of left upper lobe bronchus (arrow). The contrast medium-filled bronchi below this are branches of the lower lobe. This type of obstruction associated with a mass is characteristic of carcinoma.

and the tumor proved to be a bronchiolar (alveolar cell) carcinoma of the left upper lobe.

It is amazing to see how some of these cases are permitted to go on without surgical intervention. Recently I saw a man who was first seen in one hospital in 1942. The films showed nothing in his lungs. Five years later he was seen in another hospital. At this time a faint shadow was overlooked. He had, of course, no pulmonary symptoms; these were simply routine films. In 1948, one year later, the shadow had increased 25 per cent in size but nothing was done. In 1950, three years after the first x-ray sign, the shadow had increased a little more but still nothing was done.

Then, in 1951, over four years after the shadow first appeared, a film made in another hospital showed a much larger shadow, coming closer and closer to the center of the lung. He was subjected to a proper x-ray examination, that is, with planigraphy, and again there was found this notch which we feel is so significant that we believe it almost invariably connotes carcinoma.

Not being satisfied even with that, a bronchogram was made and the branch bronchus from which this lesion arose was seen to be obstructed and deformed just as it entered the shadow. It was the typical rattail deformity of the branch bronchus which, when seen in the bronchogram, is so characteristic that it is almost pathognomonic of carcinoma. This is the kind of lesion that cannot be reached with the bronchoscope; it is the kind which very often does not shed cells. One has to do an exploratory thoracotomy if it cannot be proved by any other means. However, we should first exhaust all the means at our disposal and have a really good, cogent reason for doing exploratory thoracotomy, as was the case here. This, of course, was a squamous cell carcinoma.

The same reasoning holds true in cases of enlargement of the hilus, of which I spoke. Let me cite the case of a patient with coronary disease—no pulmonary symptoms at all—having roentgenologic examinations because of the heart. On the first examination (figure 11a) an enlargement of the hilus on the left side was overlooked which should have been observed if the two sides had been properly compared. A year and a half later, he was still having trouble with his heart, still having films made, still with no pulmonary symptoms, but the hilus was more enlarged than before and the striking difference between the two sides was even more marked (figure 11b). Here we see what happens in carcinoma of the lung, as in many other carcinomas. The patient goes along for a year and a half that we know of (we don't know how far back this goes) without symptoms, without much change, and then suddenly, shortly after the last film which was 18 months after the first one, he begins to have a little pain in the chest, a little cough, and nine months later a roentgenogram discloses a tremendous enlargement with a mass which is even lobulated (figure 11c). The increase in size in nine months was striking. The mass was seen in the lateral view as well. If there should be any doubt as to the nature of such a mass, usually bronchoscopy will reveal its source. Nevertheless, if this is an upper lobe lesion, as this proved to be, a bronchogram may be necessary. With the contrast medium we then demonstrated a stenosis of the upper lobe bronchus in association with this mass (figure 12). Then the diagnosis is unequivocal.

I have not been able to cover all the various features of the identification of these lesions. However, I would like to leave you with these thoughts: (1) X-ray examination, either by a simple photofluorographic process or as a full-sized single posteroanterior view of the chest, is a superb instrument for detecting a disease process in the lung, particularly such a disease as carcinoma; (2) the identification of this disease process as carcinoma requires a very much more elaborate, extensive type of study, namely, films of the chest made in a variety of positions, in both phases of respiration, by means of planigraphy and, finally, if necessary, bronchography, which will often lead to signs so characteristic of carcinoma that they are almost sufficient to make the diagnosis definite and certainly sufficient to urge operation; (3) we should exhaust all these efforts in every case where any suspicion has arisen.

Carcinoma In Situ: A Concept of Cancer Without Invasion

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Introduction

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THE term "*in situ* carcinoma," as used by pathologists, embodies a general concept of one phase in the development of invasive carcinoma. Broders,[1] in 1932, was the first to use this term and clearly define this pathologic change as a distinct neoplastic entity. It is the interpretation of this concept of disease and its application to the management of the individual case that gives rise to confusion and controversy. The frequency with which *in situ* carcinoma is seen in the uterine cervix has focused particular attention on the significance of this lesion, not only in the cervix but in other locations as well. The question has arisen as to whether the epithelial changes diagnosed as *in situ* carcinoma are truly neoplastic or whether they may not represent some physiologic change which is a reversible process. When rigid diagnostic criteria are applied,[2] the concept of *in situ* carcinoma, limited to epithelial surfaces and without invasion, is valid and is based on sound pathologic evidence.

The observation that noninvasive carcinoma (carcinoma *in situ*) does occur in many different parts of the body supports the general concept that it is, in many instances, an antecedent phase of invasive carcinoma. Of particular importance is the fact that multiple foci of origin are the rule.[3]

Although particularly concerned with this problem in the cervix, McKay, Hertig and Young's summary of the evidence for *in situ* carcinoma[4] is equally applicable to all parts of the body. They emphasize that *in situ* carcinoma "histologically . . . resembles carcinoma except that it has not invaded," and that it ". . . can be observed in the surface

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epithelium immediately adjacent to many obviously invasive carcinomas of the cervix"; further, that "the lesion has been known to progress from the *in situ* stage to proved invasive carcinoma."

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We concur with these authors that the term *in situ* carcinoma is, in general, unsatisfactory. *In situ* implies a circumscribed or localized process, which is not necessarily the case, since the pathologic changes may involve considerable areas and frequently occur in multiple foci. Other terms have been suggested, such as "incipient carcinoma," "noninvasive potential carcinoma," "preinvasive carcinoma," "intramucosal carcinoma," "Bowen's disease of the cervix," "superficial noninvasive intra-epithelial carcinoma," or "intra-epithelial carcinoma." These, however, are less clearly expressive of the fact that *in situ* carcinoma is histologically recognizable carcinoma that has not invaded; in addition, this term is the most commonly used and causes minimal confusion. The general concept of *in situ* carcinoma is a sound and reasonable one and most clearly defines the process as true malignant neoplasia without invasion.

A definition and the implications of diagnosis should be given. (See figure 1, section 1.) Practical considerations have shown that the following diagnoses most completely express the biologic potential of lesions on epithelial surfaces. The clinical indications for therapy and management in each instance should be clearly understood.

Leukoplakia (figure 1, section 2)—This term is applied to a grayish-white plaque which occurs on squamous mucous membrane surfaces. This is caused by an increase in the number of cells in the mid and outer layers of the epithelium. Despite this cellular increase, there is no cellular abnormality nor is there any essential disturbance of normal maturation. Although a certain number of carcinomas do develop in areas of leukoplakia, the condition is not of itself malignant and should not be treated as such (figure 1, section 2).

Atypical hyperplasia (figure 1, section 3)—This diagnostic term is not completely specific since it is used to designate epithelial hyperplasias of abnormal character which do not have the definitive characteristics of carcinoma. Tissues showing this type of change must be regarded with suspicion and the patient must be followed clinically. The diagnosis does not warrant the type of therapy which a diagnosis of *in situ* or invasive carcinoma would demand. However, additional studies should be made of biopsies from any suspicious areas, since both definite *in situ* carcinoma and invasive carcinoma may occur in the region of lesions of this type.

In situ *carcinoma* (figure 1, section 4)—This diagnosis indicates true carcinoma which has not invaded. All the cytologic changes and all the disturbances in maturation which characterize carcinoma must be present; these are, however, strictly limited to the normal epithelial surface areas. When this change can be shown to exist in all parts of a suspicious area, a characteristic clinical course can be expected; namely, that the potential for invasive carcinoma exists and is to be expected following a variable latent period. When this diagnosis is made from biopsy specimens of limited extent, further studies are mandatory since the *in situ* carcinoma may be only a part of an area of neoplasia which includes invasive carcinoma.

Invasive carcinoma—The full diagnostic implication of carcinoma pertains in this instance. There is autonomous growth of neoplastic cells with stromatic infiltration and a strong potential for metastasis to regional structures (figure 2, section 4). The necessity for radical therapy in this instance is obvious.

Our present purpose is to review the principal anatomic sites where the diagnosis of *in situ* carcinoma is regularly made (table 1).

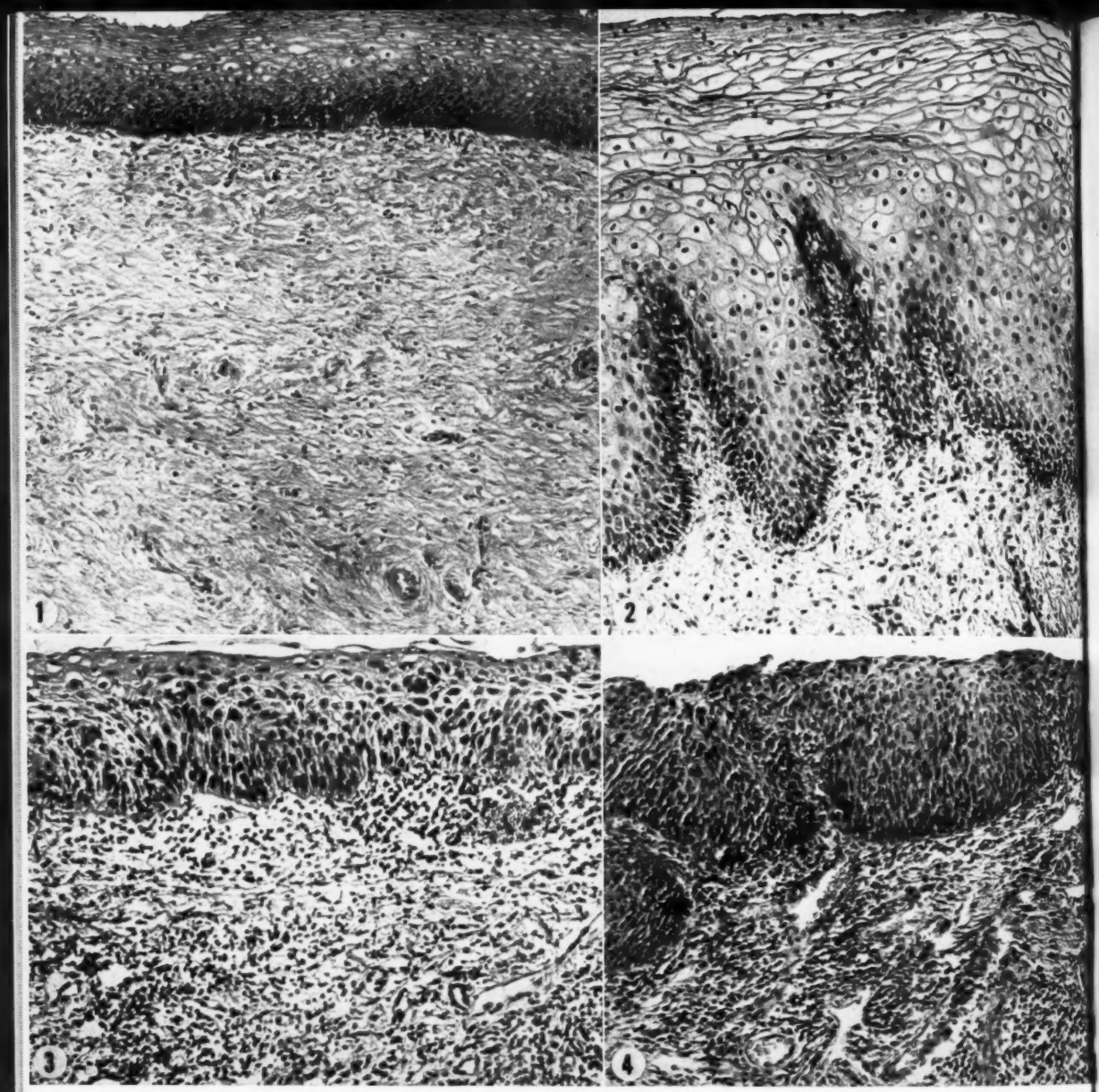


FIGURE 1. Comparison of abnormal epithelial changes and carcinoma *in situ* with normal squamous epithelium (uterine cervix).

Section 1. Normal. The squamous epithelium shows an orderly arranged basal layer with maturating cells through the first one-third of the membrane thickness, and a normal desquamating surface composed of cells having shrunken, flattened, pyknotic nuclei (hematoxylin and eosin stain, x 125).

Section 2. Leukoplakia. Note the uneven basal border with the formation of rete (peglike) structures. Unusual thickness is noted in the epithelium, and the mid and outer zones are particularly thickened. The cells in these parts retain nuclei of more or less round form and show clear vacuolation of the cytoplasm; compare this section with section 1 (hematoxylin and eosin stain, x 125).

Section 3. Atypical hyperplasia. The basal layer shows disorientation with only a few parts showing the usual orderly arrangement of basal cells. Hyperchromatism is conspicuous not only in the basal layer but also in the middle and outer thirds. A few nuclei persist into the desquamating surface (hematoxylin and eosin stain, x 125).

Section 4. In situ *carcinoma.* Note the thickness of the mucous membrane with the marked hyperchromatism of the cells extending throughout the entire layer. Nuclei of a well-formed type persist to the surface. Mitotic figures are present in the mid and outer as well as in the basal zones. The arrangement of basal cells is lost (hematoxylin and eosin stain, x 125).

TABLE 1

ANATOMIC SITES OF CARCINOMA *in Situ*

I. Epithelial surfaces
  A. Enteric cavities and communicating spaces
    1. Internal female genitalia
      a. Cervix
      b. Endometrium
    2. Breast (mammary ducts)
    3. Gastrointestinal tract
    4. Urinary tract
      a. Bladder, ureters and kidney pelves
    5. Respiratory tract
      a. Larynx, trachea and bronchial tree
  B. External
    1. Skin (Bowen's disease)
    2. Junctional nevus (melanoma)
II. Parenchymatous organs
  A. Breast (alveoli and lobules)
  B. Lung

TABLE 2

DIAGNOSIS OF CARCINOMA *in Situ* AT THE UNIVERSITY OF TEXAS M. D. ANDERSON HOSPITAL AND TUMOR INSTITUTE

(September 1, 1952 through August 31, 1954)

SITE	NUMBER
Skin	32
Lip	1
Buccal mucosa	2
Tongue	1
Tonsil	1
Larynx	6
Colon	1
Rectum	6
Appendical mucosa	1
Vagina	1
Vulva	3
Cervix	56
Breast	1
	112

TABLE 3

DISEASE CONDITIONS WHICH ARE *in Situ* CARCINOMA BUT WHICH ARE FREQUENTLY NOT SO REPORTED

1. Bowen's disease of skin
2. Certain carcinomas of the oral mucous membrane

BENIGN TUMORS WITH HIGH FREQUENCY OF *in Situ* NEOPLASTIC CHANGE

1. Junctional nevi giving rise to malignant melanoma
2. Polyps of the stomach and colon

TABLE 4

OTHER DIAGNOSES IMPLYING CARCINOMA *in Situ*

DIAGNOSIS	NUMBER
Bowen's disease of the skin	9
Squamous cell carcinoma, verrucal type	22
	31

TABLE 5

DISEASE CONDITIONS COMMONLY BELIEVED TO BE *in Situ* CARCINOMA

I. Epithelial surfaces
  A. Paget's dermatosis
    1. Nipple and areola
    2. Extramammary
  B. Erythroplasia of Queyrat
II. Parenchymatous organs
  A. Hamartomatous change (liver, kidney)

A discussion of the clinical management of such cases will be given based on the general concept that *in situ* carcinoma is, in fact, noninvasive carcinoma.

All cases diagnosed as *in situ* carcinoma at The University of Texas M. D. Anderson Hospital and Tumor Institute during the last two years have been collected for study (table 2). Consideration has also been given to the conditions frequently confused with *in situ* carcinoma (tables 3 and 4), and conversely to those diseases which are, in reality, *in situ* carcinoma but which are not usually so diagnosed (table 5). All these various types of carcinoma *in situ* will be discussed in the following sections.

The Concept of in Situ *Carcinoma in Various Anatomic Sites*

By definition, *in situ* carcinoma is restricted to neoplastic changes in the various epithelial tissues[5] and therefore does not occur in the supporting tissues of the body, such as bone, cartilage, connective tissue, bone marrow, etc. If a comparable term were to be utilized for a similar neoplastic change in the mesenchymal

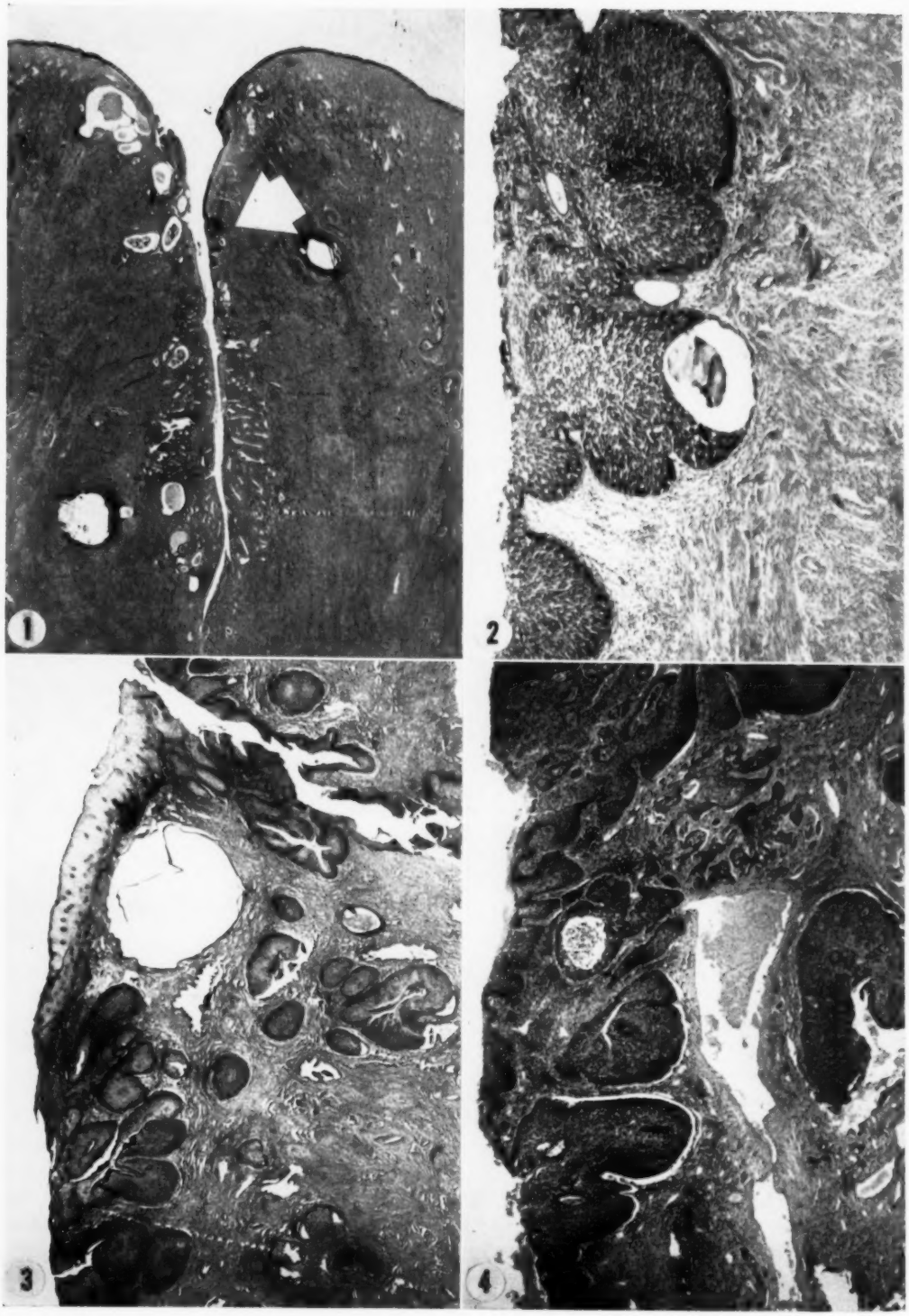


FIGURE 2. Carcinoma *in situ* of the cervix, associated with leukoplakia and transition phases to invasive carcinoma.

Section 1. This is a subserial section of a cervix showing the cervical canal. On the right upper part of the section showing the cervical lip and canal, *in situ* carcinoma is clearly noted and characterized by a deep basophilic staining of the epithelium. This extends from the inner part of the cervical canal to the outer part of the portio vaginalis. For comparison, the left upper part of the section shows normal-appearing epithelium that does not take an intense basophilic stain and which is in sharp comparison with the *in situ* changes above. Note the mass of *in situ* carcinoma (marked by arrow) representing this change that has involved the mucous glands in the endocervix. This must be differentiated with higher power magnification from invasive carcinoma (hematoxylin and eosin stain, x 5).

Section 2. This is a higher power magnification of section 1 from the area indicated by the arrow. This shows hyperchromatic, disorganized squamous epithelium characteristic of *in situ* carcinoma. The apparent extension into the underlying tissues is not invasion, but represents replacement of the epithelium of mucous glands in the area by the metaplastic *in situ* neoplastic change (hematoxylin and eosin stain, x 40).

Section 3. This section of the cervix shows the association of leukoplakia with *in situ* carcinoma. In the upper left-hand part of the section, the squamous epithelium is remarkably thickened. The more basophilic masses of epithelium seen extending from this area to the left outer margin represent *in situ* carcinoma that has developed from metaplasia of the columnar epithelium in the mucous glands of the cervix. Other masses of epithelium shown in this section are not invasive carcinoma, but squamous metaplasia in cervical glands (hematoxylin and eosin stain, x 65).

Section 4. This section shows *in situ* squamous carcinoma with extensions into the mucous glands of the cervix in a pattern similar to that demonstrated in sections 2 and 3. The section is noteworthy in that areas of invasive carcinoma are present. A transition phase from the overlying epithelium which shows *in situ* change can be seen in the upper central area. Small irregular islands of invasive carcinoma are noted through the upper half and in the central part of the section (hematoxylin and eosin stain, x 25).

tissue, it would be "*in situ* sarcoma." We know of no example of malignant transformation without invasion which occurs in mesenchymal tissue.

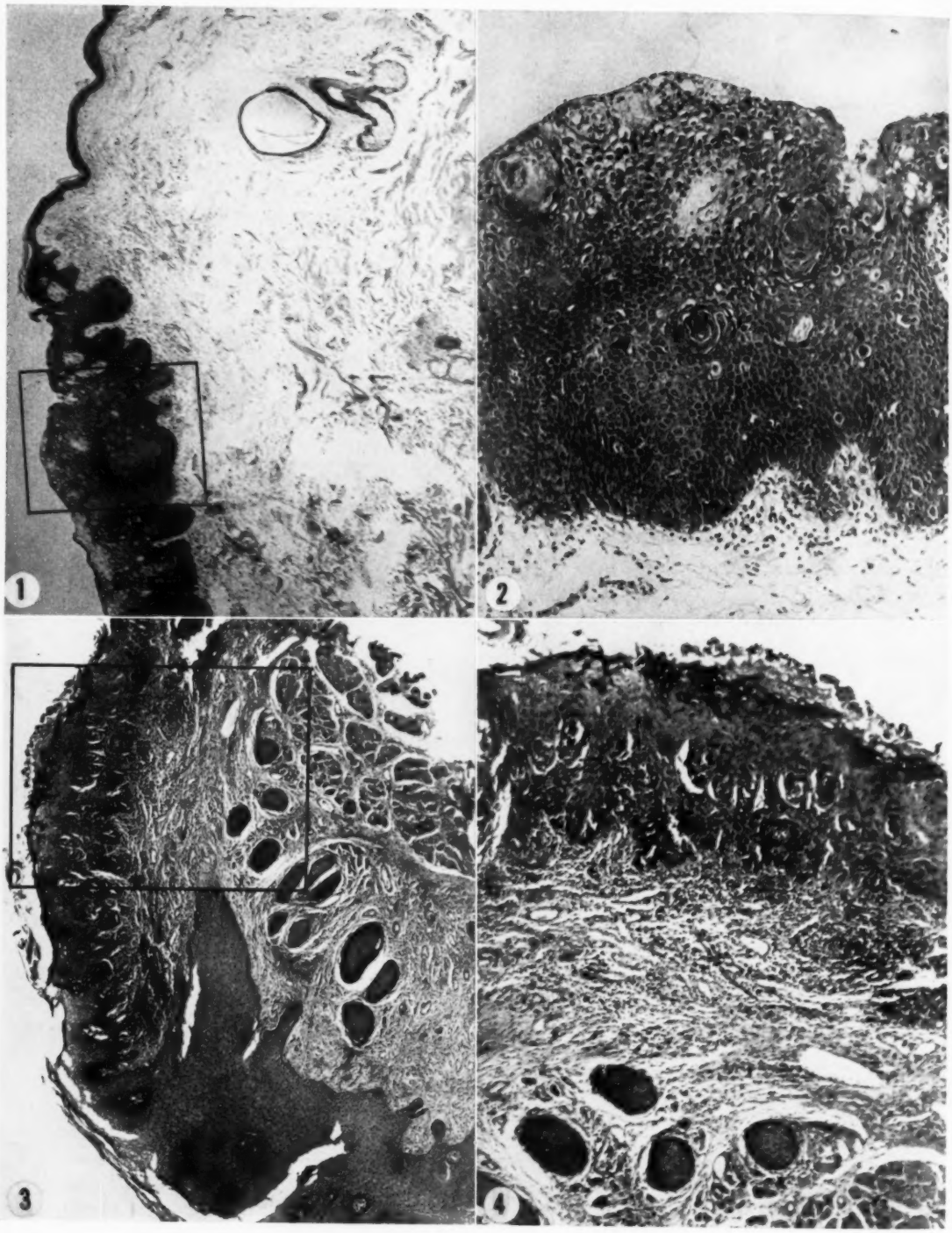
Breast and lung are the only two parenchymatous organs where *in situ* carcinoma is seen. *In situ* carcinoma of parenchymatous tissues, since it is usually discovered incidental to complete excision of the organ, does not raise problems of clinical care and management as are occasioned by the occurrence of the disease in such epithelial surfaces as the cervix and endometrium, the oral cavity, and the gastrointestinal tract.

The diagnosis and clinical significance of *in situ* carcinoma, as typified in the uterine cervix, will be emphasized. For more complete consideration of this subject, the work of Stoddard[6] may be consulted. The occurrence of *in situ* carcinoma in the less frequent anatomic sites, of which the endometrium and the gastrointestinal tract are clinically the most important, will also be discussed. In particular, the relationship of polyps of the colon to invasive carcinoma of the colon will be reviewed. Since papillomas of the urinary bladder are a special case, for which a diagnostic terminology having specific clinical significance has been devised, these, too, will be included.

Mention is also made in the present context of a relatively nonaggressive neoplastic lesion of the oral cavity which has been assigned the specific diagnostic cognomen of "verrucal squamous cell carcinoma" by Ackerman[7] (figure 3, sections 3 and 4). This regularly is preceded by changes of leukoplakia and atypical hyperplasia. Because biologically many of these lesions show little propensity for extension beyond the immediate stromatic background of the surface change, we often regard this process as having the potential of carcinoma *in situ* when considered for clinical therapy.

There are two other general anatomic sites in which *in situ* carcinoma, as such, occurs. These are the skin and vulva. Such lesions of the skin form a specific clinical entity known as Bowen's disease. Over the vulva, multiple foci of squamous cell *in situ* carcinoma as well as invasive squamous carcinoma may occur, usually superimposed on a preceding postmenopausal atrophic change known as kraurosis vulvae.

From a pathologic point of view, junctional nevi are not strictly comparable with *in situ* carcinoma, but from a clinical point of view, they fall within the broader aspects of the con-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2
3
4

FIGURE 3. *In situ* squamous carcinoma of the skin (Bowen's disease) and *in situ* squamous carcinoma of buccal mucous membrane associated with foci of invasive squamous carcinoma.

Section 1. This section of skin shows atrophic epidermis in the upper left field with transition to a markedly thickened epithelial surface characteristic of Bowen's disease. Note the accentuation of rete pegs and the lack of maturation of cells (hematoxylin and eosin stain, x 50).

Section 2. This section, taken from the area marked in section 1, shows in detail the characteristic changes of *in situ* carcinoma of squamous epithelium of a cutaneous type. Note the loss of regularly arranged basal cells and the enlarged rete pegs. Deeply stained and prominent cells of the basal type extend through the entire thickness of epithelium. In only a few areas, in the upper left-hand corner particularly, do the cells show maturation to a more normal type of squamous cell. Mitotic figures in giant cells appear in the epithelial cells outside of the basal zone in the middle and outer parts (hematoxylin and eosin stain, x 150).

Section 3. This section shows leukoplakia and *in situ* squamous carcinoma occurring in the buccal mucous membrane. In addition, foci of well-differentiated invasive carcinoma (squamous) are present in the underlying soft tissue. Leukoplakia shown in the lower half of the section is characterized by markedly thickened epithelium. In the left upper field and extending from the lower part of the section is *in situ* squamous carcinoma, showing irregularity of the basal border and hyperchromatism. Oval masses of well-differentiated squamous carcinoma can be noted in the central part. These have extended from the overlying neoplastic epithelium and infiltrate bundles of striated muscle, as shown in the area marked by the square (hematoxylin and eosin stain, x 35).

Section 4. This is a higher power magnification of that part of section 3 marked by the square to show better the atypical changes characteristic of *in situ* squamous carcinoma and the foci of invasive squamous carcinoma present in voluntary muscle (hematoxylin and eosin stain, x 75).

cept of noninvasive neoplasia. The reasons for including this relationship in the present context will be discussed.

There are, as well, certain characteristic disease processes having the dignity of clinical entities which are often confused with *in situ* carcinoma within the limits of the definition and concept which have been expressed. These include Paget's disease of the nipple, which in our opinion represents an intra-epithelial metastasis of adenocarcinoma, and the erythroplasia of Queyrat of the penis, which does not have the true histologic and cytologic characteristics of *in situ* neoplasia. These conditions will be considered separately.

In situ carcinoma should be used as a general concept of disease having a biologic character distinct from that of obvious invasive carcinoma. Utilized in this manner, the diagnosis implies possible or even probable invasive carcinoma regional to the biopsy so diagnosed. Lesions having this connotation are encountered particularly in the larynx, the bronchi and the oral cavity.

In situ carcinoma may also be found in the breast, but it seldom presents problems in clinical management and will not be discussed in this text.

Anatomic Sites Showing Definitive Carcinoma in Situ

Cervix (figures 1 and 2)—Carcinoma *in situ* in the uterine cervix has probably received more consideration by American gynecologists than any other single subject during the past decade.[8] This diagnosis in the cervix of itself is often difficult and the occurrence of *in situ* carcinoma with pregnancy presents a formidable clinical problem.

The choice of therapeutic methods must also be evaluated, since frequently radiation is the treatment of choice. This is a well-established carcinogenic factor, and as the patients with this diagnosis tend to be in a younger age group than other cancer patients,[9] therapy by radiation in itself poses an additional problem because of their greater life expectancy.

Carcinoma *in situ* of the cervix is a definite pathologic entity with a well-established clinical significance (figure 2, section 1). It is important, however, that there be a consistent pathologic interpretation of the lesion so that the attending physician will always have a definite attitude toward its implications. A variety of terms has been used for those changes not thought to be sufficiently characteristic to warrant the diagnosis of *in situ* carcinoma, e.g., "atypical hyperplasia," "precancerous epithelial hyperplasia," "hyperplasia of squamous epithelium with atypical change." This type of pathologic change, although not *in situ* carcinoma, is also impor-

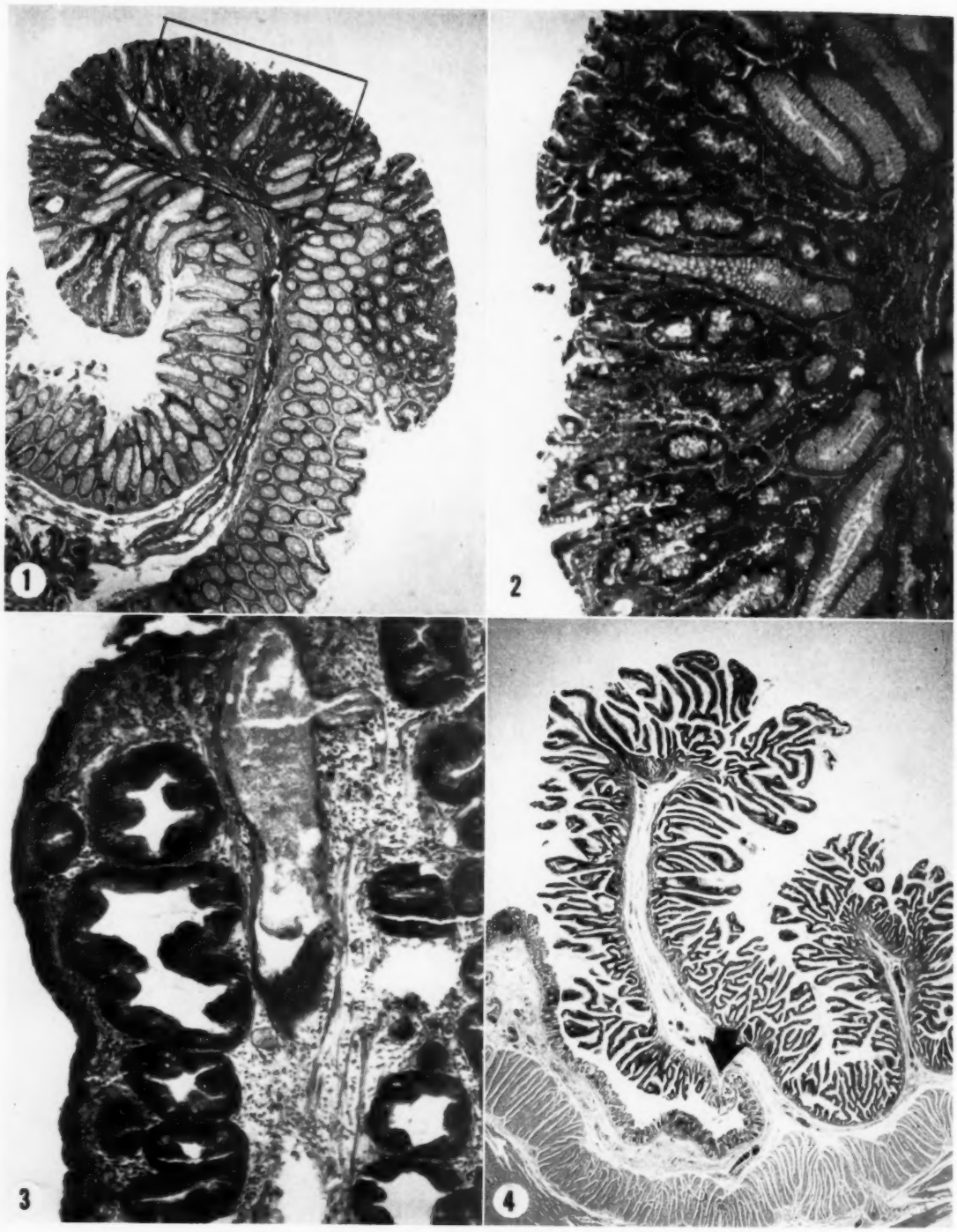
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FIGURE 4. Adenomatous polyps and polyps of the large intestine showing atypical change for consideration with examples of *in situ* carcinoma.

Section 1. This small adenomatous polyp was one of many adenomatous polyps, all of larger dimensions, found in a segment of colon resected for invasive adenomatous carcinoma. This section illustrates well the transition of normal-appearing mucous glands (shown in the section as light-staining) to true adenomatous changes (shown best on the surface as darker-staining areas). The glands characterizing the adenomatous change are orderly in their arrangement and can be differentiated from the normal glands only by their hyperchromatic staining qualities (hematoxylin and eosin stain, x 25).

Section 2. This is a higher power magnification of section 1 of the area marked by the square. This shows better the transition of the glands from the normal-appearing types to the hyperchromatic atypical ones shown in the central part of the photograph, that characterize the adenomatous polyp (hematoxylin and eosin stain, x 75).

Section 3. This is a section from an adenomatous polyp showing advanced atypical change in the epithelial cells. Note the deep hyperchromatic-staining quality and stratification of the nuclei. In many instances the nuclei are so abundant that they occupy nearly the entire thickness of what would normally be the columnar, mucus-secreting epithelial layer (hematoxylin and eosin stain, x 150).

Section 4. This section taken from a papillary adenoma of the rectum shows the junction of the adenoma with normal mucous membrane of the rectum. This is marked in the section. Note the usual depth of the epithelium as seen on the left, and compare it with the papillary, markedly folded change which characterizes the papillary adenoma. The cells of the papillary adenoma showed changes of *in situ* carcinoma and, as demonstrated in this section, stain deeply chromatic. This was taken from foci of *in situ* changes occurring in a papillary adenoma (hematoxylin and eosin stain, x 7).

tant in managing the individual case[10] (figure 1, section 3). The patient must be followed clinically since it has been shown that this change frequently antedates the development of characteristic *in situ* carcinoma, or may be adjacent to areas having the established changes of *in situ* carcinoma.

Pathologic changes in the uterine cervix in pregnancy have been extensively and completely studied by Murphy and Herbut,[11] Nesbitt and Hellman,[12] Peckham and associates,[13,14] Schleifstein[15] and Danforth.[16] These studies demonstrate that pregnancy produces characteristic changes in cervical tissue, which include hyperactivity of the basal cell layer of squamous epithelium and epidermidalization of endocervical structures. These changes, although superficially similar to the atypical changes of *in situ* carcinoma, are apparently not concerned with their initiation, since they are known to regress and disappear shortly after parturition, certainly within 28 weeks thereafter. Where definite *in situ* carcinoma has been demonstrated either prior to or during pregnancy, these changes have persisted in the same degree both following a particular delivery and in some instances after several deliveries. The characteristic changes of *in situ* carcinoma, once established, can therefore be regarded as nonreversible and independent of the influence of hormones during pregnancy.[17]

What is the treatment for *in situ* carcinoma in the nonpregnant woman? Since *in situ* carcinoma must be accepted as a form of cancer and the most widely accepted plan of cancer therapy is, where possible, extirpation of the neoplastic cells from the body, removal of those areas having the *in situ* change, either by electrocoagulation or by cold-knife conization, should be accomplished. Of the two methods, Thornton and associates[18] and Carter[19] have considered cold-knife conization to be preferable, principally because of its precision and the fact that once the tissue is removed, more complete and definitive pathologic study is possible (figure 2, section 2). If the pathologic studies on multiple sections of the conization by subserial technics demonstrate only *in situ* carcinoma, careful clinical follow-up of well over six months[20] is all that is needed. On the other hand, if foci of invasive carcinoma are demonstrated by the pathologist's study of the tissue, the usual more radical radiation or surgical procedures for therapy of carcinoma of the cervix should then be instituted. When the woman is past or near the menopausal age, consideration should be given to the performance of a total hysterectomy, provided, of course, a prior conization has not demonstrated invasive carcinoma. No matter how small a focus of invasive carcinoma may be, a strong possibility

exists for lymphatic spread or direct extension to contiguous tissues.

What is to be the management of the case where a diagnosis of *in situ* carcinoma is made in the pregnant woman? The final management in this special case is contingent on, and dictated by, not only the opinions and usual methods of the attending physician but also the personal feelings and desires of the patient in regard to present and future pregnancies. Since it has been well established that *in situ* carcinoma may remain noninvasive for from 1 to 12 years,[21] the patient, in the interest of obtaining subsequent pregnancies, may wish not to have any therapy performed. On the other hand, a patient in the first trimester of pregnancy may not wish to take the risk of developing invasive carcinoma and may prefer to have the pregnancy interrupted and the therapeutic procedures for *in situ* carcinoma undertaken.

Endometrium—The diagnosis of *in situ* carcinoma in the endometrium is infrequently encountered in clinical records. Nevertheless, the concept of noninvasive malignant neoplasia still obtains and can be observed in this tissue. In the usual parlance of the pathologist, certain abnormal changes found in endometrial glands are termed "atypical" hyperplasia. This term is often nonspecific since it is used for a variety of pathologic changes; critically applied, it implies a type of change not sufficiently advanced to be called neoplasia but still having some of its features.

In 1949 Hertig and Sommers[22-24] reported a significantly high incidence of endometrial polyps, cystic hyperplasia and adenomatous hyperplasia occurring in women who 6 to 13 years later developed endometrial carcinoma. Adenomatous hyperplasia, showing neoplastic tendencies, was observed three to five years before the cancer developed and was regarded as being particularly significant. These changes could not be considered as irreversible but a relationship to definite *in situ* carcinoma and invasive carcinoma was evident. *In situ* endometrial carcinoma, as summarized by McKay[25] from Hertig's work, is a decided and clear-cut pathologic entity.

The work of Hertig is fundamental and has oriented medical thought to regard the endometrium, as well as the cervix, as a source of *in situ* carcinoma. Pathologic examination of the endometrium in a woman who has had irregular menses or postmenopausal bleeding should be made with the same concern and thought for therapy as for *in situ* carcinoma of the cervix. As with the cervix, a latent period of from one to five years passes before the development of invasive carcinoma can be determined by biopsy. A frequent association with obesity, diabetes mellitus and nulliparity suggests a common metabolic background of hormonal abnormality. Orrahood and Wyatt[26] conclude that the disease proceeds by morphologic transition from cystic endometrial hyperplasia through adenomatous hyperplasia, into *in situ* carcinoma, and eventually into adenocarcinoma of the endometrium.

Gastrointestinal tract (stomach and colon) (figure 4)—The principal lesions of the gastrointestinal tract where the question of *in situ* carcinoma arises are polyps of the stomach and of the colon.

Polyps of the stomach may be multiple, with polypoid or sessile masses involving nearly all parts of the stomach, or they may be present as a single large mass with a pedunculate stump. Polyps of the stomach may show *in situ* carcinoma in one or several foci, but unless invasive carcinoma can be demonstrated, there would be no reason to institute more than the usual follow-up if the polyp and its stalk and base had been removed.

In situ carcinoma of the colon presents nearly the same problems as pertain for the stomach. Although Ravdin and Ravdin[27] report Helwig as having clearly demonstrated that carcinoma of the colon may arise from areas of *in situ* neoplasia in nonadenomatous mucosa, it is widely accepted that nearly all carcinoma of the colon arises in a pre-existing adenomatous polyp. Adenomatous polyps (figure 4, sections 1, 2 and 3) are to be distinguished from pseudopolyps of inflammatory or other causation in that they represent benign neoplastic change and are in the strict sense of the word true tumors.

We share the opinion expressed by Willis[28] and Helwig[29,30] that adenomatous polyps both

of the colon and of the stomach represent but one phase in the development of carcinoma in these tissues. It is not known for certain if all of them possess the potential to become invasive cancer, but a number sufficiently large to justify this concept are known to do so. The figures of Ackerman and Del Regato[31] show that invasive carcinomas of the colon occur in the following incidence by location: 76 per cent in the rectum and sigmoid, 12 per cent on the right side, 6 per cent in the transverse colon, and 6 per cent in the descending colon. The incidence of carcinoma as shown from these figures closely parallels the incidence by location of polyps observed in the study made by Helwig on colons removed at autopsy.

The problem of clinical management interjects itself into the treatment of colon cancer when a diagnosis of *in situ* carcinoma is returned with that of an adenomatous polyp. This is particularly true of the biopsy specimens removed from the rectum and rectosigmoid areas where only fragments or, only occasionally, the whole polyp is removed for pathologic study. If the *in situ* neoplasia is present on the tip of the polyp, there should be no reason for concern and the case would be treated as benign, provided the whole polyp and its pedicle can be visualized. If, on the other hand, the tissue examined is composed of multiple fragments of polyp, which prevent orientation of the pieces as to the base, and *in situ* carcinoma is seen in one of these, it is impossible to be certain that the *in situ* change is not still present in an area adjacent to the mucosa. In such cases, local resection of the area with further examination would be recommended.

In a high percentage of cases it is possible for the pathologist to determine, in a polyp removed for frozen-section diagnosis, whether *in situ* carcinoma or invasive carcinoma is present. When it is possible to make the diagnosis at the time of operation, the operative procedure to be undertaken can be readily determined by consultation between the pathologist and the surgeon. If the carcinoma is obviously invasive, the usual resection should be done; where the *in situ* change is restricted to the tip of a polyp, as in the case mentioned before, local resection of the polyp and adjacent mucous membrane would be sufficient.

The papillary adenoma (figure 4, section 4) found almost exclusively in the rectal ampulla is an interesting neoplastic condition that should be regarded as *in situ* carcinoma. This disease is frequently confused with invasive carcinoma by attending physicians, and occasionally it is not possible for the pathologist to make the correct diagnosis from small biopsy specimens. It is most important that the diagnosis of papillary adenoma be established prior to operation, because the surgeon is justified in performing a less radical procedure for this condition if anatomic considerations in regard to the location of the tumor will permit. A small percentage of these papillary adenomatous tumors undergo malignant change to invasive carcinoma.

Urinary tract—In considering the urinary tract, the transitional epithelium of the kidney pelves, the ureters, the bladder and the urethra will be discussed.

Here a mucous membrane surface is constantly bathed by a flow of urine, and it might therefore be expected that the development of carcinoma on the surface may be the result of some as yet unidentifiable carcinogenic substance concentrated in the urine. This is known to occur in the case of aniline dye workers where aniline derivatives excreted in the urine produce a high incidence of bladder carcinoma.

In situ carcinoma occurring in the transitional epithelium of the urinary tract is a problem in histologic interpretation which arises most frequently in the urinary bladder. Because of the tendency for recurrence of the so-called benign transitional cell papillomas of the urinary bladder, the American Registry of Pathology[32] has adopted the term "transitional cell carcinoma grade I" for all lesions falling into this group. For this reason, in many institutions a diagnosis of transitional papilloma or *in situ* carcinoma of the urinary bladder has largely disappeared from case records. This appears reasonable and sound, since due to the fragmentary nature of the specimens removed, pathologists cannot definitely

ascertain which papillomas will recur and which are a benign phase of neoplasia. More probably the general concept should be that transitional cell carcinoma in the bladder has its inception as the most benign form of the disease—the transitional cell papilloma. Moreover, this general concept of the transitional cell papilloma of the urinary bladder is in complete keeping with the concept of *in situ* carcinoma; namely, that it does occur and should be treated as such.

Skin (Bowen's disease) (figure 3, sections 1 and 2)—In 1912, Bowen[33] described an atypical proliferating lesion of skin that has since come to be known as Bowen's disease. In a later consideration of this lesion, Darier suggested that it be called Bowen's disease because of Bowen's prior description. To Darier, however, goes the credit for recognizing this disease as *in situ* carcinoma and a truly neoplastic condition.

Its most frequent occurrence is on the unexposed surfaces of the skin, but it has been described occasionally on other parts. The lesion is characterized clinically by a slightly raised, plaquelike lesion that may progress over a period of years if untreated. Microscopic study will disclose the typical changes of *in situ* squamous carcinoma. Lesions of this type have been observed to be present from 5 to 35 years.

We concur in the opinion of Montgomery[34] that this is in fact *in situ* squamous carcinoma and that the lesion may ultimately progress to infiltrating carcinoma. The question of whether or not metastases from the noninfiltrating type of Bowen's disease can take place has received attention from several authors in the literature, but we adhere to Stout's[35] concept that metastases cannot occur without invasion in some part of the primary lesion. Such foci may be small, as Stout has pointed out, and may actually escape microscopic detection.

Some authors would reserve the term Bowen's disease for the characteristic circumscribed, slowly progressing skin lesion. Others, however, have applied the term Bowen's disease to *in situ* carcinoma found any place in the body (cervix, respiratory tract, genitourinary tract, and others).[36] We feel that the cutaneous disease, as originally described by Bowen, represents a characteristic clinical and pathologic entity of *in situ* neoplasia of skin, and that its use for *in situ* carcinoma as it occurs in other sites in the body is only confusing.

Skin (kraurosis vulvae and in situ *carcinoma of the vulva)*—Closely related to the concept of Bowen's disease of the skin is the *in situ* carcinoma which develops in postmenopausal women, usually associated with the syndrome known as kraurosis vulvae. This condition, which occurs primarily in postmenopausal women, undoubtedly is dependent on endocrine factors associated with the menopause. The development of leukoplakia with areas of *in situ* carcinoma which progress to carcinoma of an invasive type is but one phase of the total clinical picture. Contraction and fibrosis of the subepithelial connective tissue produce the shrinkage, induration and epithelial atrophy which are so characteristic of this disease and form the basis for its name. It does not appear likely that the subepithelial connective tissue change has any relationship to the epithelial changes which may progress to invasive carcinoma. It is probably an effect of the same factor (hormone), acting on two separate tissues which are in juxtaposition and serve a common body function. The most important clinical consideration is that neoplastic lesions in this area tend to be multiple and new lesions tend to appear with passing time. Once this condition becomes established, the whole vulval area appears predisposed to potential neoplasia.

Junctional nevus (malignant melanoma)—To the pathologist, the diagnosis of malignant transformation in a junctional nevus presents one of the most difficult problems in histopathologic diagnosis of cancer. When these atypical changes warrant the diagnosis of malignant melanoma, with the connotation of probable distant metastasis, the opinion of the most experienced pathologic consultant should be solicited. Even with extensive experience, a singularly significant number, estimated to be 5 per cent, will fall into an indeterminate group. It must be accepted that

cells of the junctional nevus type which appear entirely restricted to the epithelium may undergo malignant transformation and produce distant metastases. In fact, the 12 to 20 per cent of cases of malignant melanoma where no primary focus has been demonstrated have been regarded as falling into this category—namely, a malignant transformation that has not infiltrated locally but has given rise to distant metastases.

This problem is particularly difficult for the pathologist, since he is usually able to examine only a sample tissue that is removed, and he never knows but that a few hundred microns farther into the area sampled there may not be ample evidence of the true neoplastic change so characteristic that the diagnosis would be obvious. Many times in a junctional nevus, only one focus will show sufficient change to be regarded as malignant melanoma. Fortunately, this situation does not usually exist with other types of *in situ* neoplasia, since an essentially *in situ* change is not attended by the hazard of distant metastasis which characterizes the histologic behavior of melanoma.

Diseases Often Confused With in Situ *Carcinoma*

In this group are Paget's dermatosis and the erythroplasia of Queyrat. Not infrequently, the working concept is carried by physicians that these conditions represent *in situ* carcinoma. This is not the case.

Paget's dermatosis—Paget,[37] in 1894, described a chronic type of dermatitis occurring in the nipple and areola of women which is often later associated with obvious malignant tumor. Originally this chronic skin irritation was thought to constitute a form of cancer developing in the skin with secondary spread to the underlying breast tissues. Since that time there has been voluminous literature on the pathogenesis and relationship of this condition to neoplastic disease of the breast. The concept presented here has been adequately documented by the significant studies of Inglis[38] and Dockerty and Harrington.[39]

These studies indicate that in Paget's disease of the nipple, it is probable that the lactiferous ducts and adjacent areas undergo malignant transformation, and that through intra-epithelial spread of the tumor cells the cutaneous surfaces of the nipple and the areola are involved.

Paget's disease not only occurs in the nipple and areola but is seen in extramammary locations, principally in the axillae and the perineum. In these areas, which are along the "milk line" of the body, apocrine glands are usually present in abundance. The concept of extramammary Paget's disease has been accepted, and in the studies of Plachta and Speer,[40] serial sections have indicated an underlying carcinoma with extension to the overlying epithelial surface. Since extramammary Paget's disease is always found in skin areas in which apocrine glands are present, it has the same biologic mechanism as Paget's disease of the breast, namely, that it arises in apocrine ducts and has the ability to metastasize to epidermis and to cause characteristic skin manifestations. It is now accepted by Bowman and Hartman,[41] as well as by others, that the skin manifestations of Paget's disease in this location are not *in situ* carcinoma developing *de novo* in this tissue, but rather a chronic dermatitis and inflammatory condition in the skin caused by intra-epithelial metastases of malignant tumor cells from the underlying carcinoma.

Erythroplasia of Queyrat—Paget (1874), Parnowsky (1891) and Fournier and Darier (1893) first described erythroplasialike lesions on the penis; however, because the disease was so completely studied and described by Queyrat in 1911, it since has been known by the eponym "erythroplasia of Queyrat." Although Klinger and Northrip[42] state that this disease may occur in numerous locations, including the clitoris, vulva and buccal mucosa, its most frequent appearance is on the glans penis.

Erythroplasia of Queyrat is characterized by a superficial, irregular but sharply demarcated, oval lesion with a reddened, shiny appearance and a somewhat firmer consistency than the surrounding normal skin. A single lesion is present in most cases, although at times several lesions have been noted. The

plaque may remain stationary for a varying amount of time, then increase in size. Rarely, a temporary regression is observed.

Histopathologically, the lesion is characterized by acanthotic changes, edema, vascular dilatation and marginal infiltrations in the dermis by inflammatory cells. Because the cytologic changes of a neoplastic nature utilized by pathologists to make a diagnosis of *in situ* carcinoma are notably absent, this disease cannot be regarded as *in situ* carcinoma. According to Montgomery (as cited by Merricks and Cottrell[43]), 20 per cent of such cases eventually develop into squamous carcinoma.

Summary

In situ carcinoma is a clinical and pathologic entity which occurs only in the epithelial cells of the body. Histologically it is carcinoma, except that it has not invaded, and it therefore represents one phase in the development of invasive carcinoma. The pathologic changes usually involve considerable areas and frequently occur in multiple foci.

In situ carcinoma must be distinguished from atypical but reversible physiologic changes by applying rigid and definite histologic criteria. Before a diagnosis of *in situ* carcinoma is made, the evidence of neoplastic change in the cells should be unequivocal. In no instance should a positive diagnosis of *in situ* carcinoma be made without microscopic examination, and multiple biopsies should be taken for study to exclude, as fully as possible, the coexistence of invasive carcinoma.

Confusion as to the significance of pathologic terms may result in the loss of the full import of the diagnosis of *in situ* carcinoma; namely, that it is cancer and cannot be temporized with. The importance of the use of a standardized terminology and the need for complete understanding between the pathologist and the attending physician as to the significance and therapeutic implications of such a diagnosis cannot be overemphasized. This can be achieved only through close collaboration between the two, and should include consultation on each individual case.

Theoretically, any epithelial surface can manifest the changes of *in situ* carcinoma; however, it is recognized with some frequency in only a few of many potential locations. Anatomic sites in which it has been described are the uterine cervix, the endometrium, the oral cavity, the gastrointestinal and urinary tracts, the skin, and certain of the parenchymatous organs such as breast and lung. No comparable *in situ* neoplastic change is seen in the mesenchymal tissues. The frequency of its development on the external surfaces of the body suggests the possibility of the influence of some carcinogenic substance of exogenous origin—e.g., in the external environment or excreted in the body fluids.

The treatment of *in situ* carcinoma in any site is the same as for any type of cancer, namely, the eradication or removal of the neoplastic cells. Because of the absence of invasion, therapy may be less radical, and surgical excision is considered the treatment of choice. Subsequent examination of multiple sections of the tissue removed is considered advisable.

The problem of establishing a diagnosis of *in situ* carcinoma occurs most frequently in the uterine cervix where it is further complicated by pregnancy. *In situ* carcinoma in the uterine cervix is a definite pathologic entity and should not be confused with those characteristic changes which occur in cervical tissue during pregnancy. Once the diagnosis is established, the tissue changes can be regarded as nonreversible and independent of the influence of hormones during pregnancy.

Cases of *in situ* carcinoma offer the best prognosis of any type of cancer; however, the patient must be carefully watched for a long period of time because of the multiplicity of potentially malignant lesions seen in cases of this type.

Certain disease entities are not always recognized as *in situ* carcinoma although this should be the diagnostic implication. Bowen's disease of skin is always *in situ* squamous carcinoma. A special category of squamous carcinoma in the oral cavity, the verrucal type, is treated as an *in situ* carcinoma in that only local extirpation is indicated. Two other specific lesions often show focal areas of transformation to *in situ* carcinoma and should

always be regarded with suspicion. Of these, the adenomatous polyps of the stomach and particularly of the colon are the more important. Kraurosis vulvae is rarer but shows a predisposition to develop *in situ* squamous carcinoma frequently in multiple foci. The presence of *in situ* carcinoma in either of these locations must be carefully evaluated, since in such cases invasive carcinoma is also frequent.

Junctional nevi showing atypical activity are a special class. In some instances a definitive diagnosis of a malignant melanoma cannot be made, yet the microscopic changes do not allow an unequivocal diagnosis of benign junctional nevus. Such lesions must be treated locally by wide excision and the patient followed. In this sense, certain junctional nevi must be regarded as *in situ* neoplasia.

Those diseases most frequently misinterpreted as carcinoma *in situ* are Paget's dermatosis, which is intra-epithelial metastasis of underlying carcinoma, and the erythroplasia of Queyrat which shows no neoplastic changes. The latter condition, however, may precede a true malignant transformation.

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The Intrinsic Factor of Castle

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NOT long after vitamin B_{12} was discovered to provide the action of the long-sought hematopoietic principle which is effective in producing remission of pernicious anemia, hematologists determined that this vitamin is relatively ineffective when administered orally unless the intrinsic factor of Castle is present in adequate amounts in the patient's gastric secretion or is supplied with the vitamin B_{12}. Thus, the concept which Castle and his associates had established that pernicious anemia patients have a double requirement for an extrinsic food factor and an intrinsic gastric factor was extended to identify vitamin B_{12} as the extrinsic factor. Thereafter, it was inevitable that efforts would be made to study more precisely the relationships of the extrinsic to the intrinsic factor, and to identify the latter. This report will briefly summarize the principal recent developments in these studies.

At the outset, it seems fair to state that thus far no report has appeared with convincing proof of the identification of the chemical nature of intrinsic factor. Latner and McEvoy-Bowe[1] and Latner, Merrills and Raine[2-4] have stated that they have isolated the intrinsic factor and have found that it is a mucoprotein having a molecular weight of about 15,000. The data which they have supplied are meager, and are not sufficient to permit judgment of the validity of their conclusion, but no evidence is available to show that their conclusions are incorrect. Glass[5] has stated that his studies have revealed that intrinsic factor activity is present in a gastric juice fraction which he terms the glandular mucoprotein, and he recently published a statement in which he compared his considerable data with those of Latner and his co-workers. What makes these studies so tedious and prevents the early resolution of these controversies is the difficulty of evaluating the intrinsic factor activity.

The present interest in the intrinsic factor lies in two different directions: (1) Does intrinsic factor deficiency contribute to any

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disease syndrome, possibly a hitherto unrecognized or chronic form of vitamin B_{12} deficiency, other than pernicious anemia? (2) What is the nature and mechanism of action of intrinsic factor? Since vitamin B_{12} without intrinsic factor is effective when administered parenterally in cases of pernicious anemia, the gastric factor is obviously concerned in this connection chiefly with the intestinal absorption of vitamin B_{12}. For example, Castle[6] has said, ". . . the disease (pernicious anemia) would not develop if the patient could effect daily the transfer of a millionth of a gram of vitamin B_{12} the distance of a small portion of a millimeter across the intestinal mucosa and into the blood stream. This he cannot do, principally as a result of failure of his stomach to secrete into its lumen some essential but still unknown substance. Yet the patient may each day absorb without much difficulty the products of digestion of many grams of carbohydrate, fat and protein from foods that in addition may contain consequential amounts of vitamin B_{12} in terms of his trivial need."

As the result of many studies on the oral administration of vitamin B_{12} to patients with pernicious anemia, it is clear that the intrinsic factor facilitates the intestinal absorption of vitamin B_{12}. If adequate amounts of normal gastric juice are present, the daily administration of 5 μg. of vitamin B_{12} (cyanocobalamin) produces a maximal hematopoietic response; whereas, if the intrinsic factor is not present, the daily administration of as much as 1000 μg. may be ineffective. These clinical studies have shown clearly what hematologists had earlier concluded on less definite evidence, namely, that in persons with pernicious anemia the degree of intrinsic factor deficiency or the responsiveness to oral treatment varies considerably. For example, although a daily dose of only 5 or 10 μg. of cyanocobalamin without added intrinsic factor usually does not produce a significant hematopoietic response in cases of pernicious anemia, instances of a slight to definite response have been observed, and, when the oral dose of vitamin B_{12} is increased to from 50 to 100 μg. daily, the incidence and degree of the response appear to increase. Large oral doses of vitamin B_{12} (1 to 5 mg.) without intrinsic factor have been reported to have produced remissions of pernicious anemia.

Chalmers and Hall[7] in England reported that single oral doses of from 2000 to 9000 μg. of cyanocobalamin in patients with relapsed pernicious anemia produced initial hematologic responses similar to those obtained by the intramuscular injection of from 20 to 100 μg. of cyanocobalamin, and in one patient a daily dose of 50 μg. maintained a remission. On the other hand, several reports have indicated that doses of 50 to 5000 μg. of cyanocobalamin have been ineffective in similar patients. These reports, which appear at first glance to conflict, can be interpreted to verify the earlier conclusions that the degree of deficiency of the intrinsic factor and the responsiveness of pernicious anemia patients vary considerably. Some patients appear to secrete some intrinsic factor, although not enough to prevent, under certain conditions, the relapse of the disease.

When such large amounts as 1000 μg. or more of cyanocobalamin are administered orally in one dose, and absorption of vitamin B_{12} does occur, the normal mechanism of absorption is probably bypassed by virtue of the high gradient from the intestine to the blood.[8] At first, it might appear to be simpler to resort routinely to large oral doses of vitamin B_{12}, such as more than 2000 μg. daily, were it not first for the cost of the cyanocobalamin in such quantities, and second for the possibility that bacterial mutants which consume inordinate quantities of cyanocobalamin may conceivably develop in the intestine and thus render ineffective at the time, or later, the administered vitamin B_{12}. This idea has not been verified, but it bears watching as an item of interest related to this problem.

One of the early theories of the cause of pernicious anemia was based on the finding that bacteria may flourish abnormally high in the intestinal tract and stomach of pernicious anemia patients due to the lack of acid and other gastric secretions. Recently, Burkholder isolated from the duodenal secretions of a patient with relapsed pernicious anemia an

Escherichia coli mutant which consumed large quantities of cyanocobalamin when tested in vitro. Other investigators have noted that certain bacteria isolated from the intestine may consume large quantities of vitamin B_{12}. Girdwood, at the recent Hematological Congress in Paris, presented results of his work on the influence of normal stomach juice on the absorption of vitamin B_{12} by many micro-organisms isolated from the stomach and upper part of the intestine of pernicious anemia patients. This work was undertaken to determine whether normal stomach juice would prevent the attack of the micro-organisms on the vitamin. The results of all his tests, performed in many ways, were reported to be negative. Hence, whether bacterial mutants play an important role in consuming orally administered vitamin B_{12} to render it unavailable to the subject is as yet unproved, and it will be interesting to watch for reports of further studies on this subject. Meanwhile, however, since the intrinsic factor so greatly facilitates the absorption of vitamin B_{12}, it is obviously useful as a means of rendering effective reasonably small doses of vitamin B_{12}, thus making for economy of oral therapy in all cases in which intrinsic factor therapy is desired.

Intrinsic Factor Deficiency Diseases

This leads to consideration of what conditions are accompanied by intrinsic factor deficiency of sufficient importance to warrant its use with oral therapy with vitamin B_{12}. Pernicious anemia is the classic example of disease due to intrinsic factor deficiency, and at the present time this and total gastrectomy and possibly some varieties of advanced atrophic gastritis are conditions in which one clearly can expect faulty absorption of vitamin B_{12} due to intrinsic factor deficiency.

Are there any other conditions in which intrinsic factor deficiency may contribute to disorders which have hitherto escaped identification with vitamin B_{12} or intrinsic factor? There is no present proof of such, but there are many hints which indicate that a careful survey of the probabilities merits considerable effort. Experimental studies of the role of vitamin B_{12} in animals have shown that this vitamin is of prime importance in many bodily functions, as, for example, in the utilization of protein, in bodily growth, in the functional maintenance of certain portions of the central nervous system and the hematopoietic system, and in fertility, etc., and its deficiency is manifested in different ways in different species. There is striking economy of the last stores of vitamin B_{12}, so much so that long periods of deficiency are required to render apparent any manifestations of deficiency unless possibly some secondary condition supervenes to accelerate the onset of signs of the deficiency, as, for example, infections usually accelerate the relapse of pernicious anemia patients and increase the requirement for vitamin B_{12}. Thus, disturbances which may be due to this deficiency in human beings may conceivably be subtly deceiving as to time of onset and their pattern.

At the present time, a considerable effort is being made by various investigators on both sides of the Atlantic to determine whether intrinsic factor deficiency does exist in persons other than those who have pernicious anemia or who have undergone a total gastrectomy. If one could identify persons with this deficiency, it might be possible to sort out one or more patterns of disturbances that could be observed during controlled treatment with vitamin B_{12} and the intrinsic factor. The most likely group of persons in which to seek intrinsic factor deficiency appears to be those having deficient gastric secretion as judged by other standards, as, for example, those with achlorhydria or gastric atrophy, especially in people past middle age, but without pernicious anemia.

Glass has pointed out a number of interesting correlations which suggest that, when gastric secretion is deficient, there may also be a defect in the intrinsic factor production. Alt[9] has stated that ". . . 20 to 30 per cent of patients beyond the age of 60 will have a histamine achlorhydria." A physician, having in mind the fragile appetite and obviously reduced or atrophic gastrointestinal function of many aged persons, immediately wonders whether such persons secrete sufficient intrin-

sic factor to provide for absorption of the required vitamin B_{12}. When all metabolic functions are so much reduced, does vitamin B_{12} deficiency always show itself as the classic pernicious anemia, or are some of the central nervous deteriorations and other wastage phenomena of old age due to a lack of this vitamin? One cannot be content with such necessarily vague correlations, and one must find ways to establish definitely whether the deficiency actually exists.

Appraisal of Intrinsic Factor Function

Until recently, no method for the appraisal of intrinsic factor function in an individual was available. The advent of Co^{60}-labeled cyanocobalamin provided a new tool which the ingenuity of a number of investigators has applied in three different ways. Although two of these methods are somewhat cumbersome, they all appear to provide means for estimating the degree of intrinsic factor activity in an individual, and for measuring the effectiveness of preparations containing the intrinsic factor. These methods are still under investigation, and the results of each of the methods must be correlated further with those of the others. Nevertheless, one can say with more confidence than seemed possible three years ago that the goal of detecting intrinsic factor deficiency is close at hand.

The methods mentioned have thus far employed Co^{60}-labeled cyanocobalamin, and with this goes the difficulty that since the half-life of Co^{60} is long, the dose administered must be restricted to the small amounts that have been determined to be safe. Although these amounts are indeed quite small, the gamma rays emitted by Co^{60} have sufficient penetrability to make their detection easy by a proper scintillation counting apparatus. Recently, Co^{58}, which has a satisfactorily short half-life, has been employed for similar studies, but this work has not progressed beyond the preliminary stages.

With the tagged cyanocobalamin, one can identify the vitamin B_{12} which was administered, and thus determine whether the intrinsic factor causes an increased absorption of the labeled dose. Since one measures radiocobalt, it is necessary to prove by suitable methods that the cyanocobalamin indeed is absorbed and that what is measured is not just some degraded compound of cobalt. With these problems in the background, the principal methods that are currently being employed are as follows: (1) recovery of Co^{60}-tagged cyanocobalamin from the stools;[10-13] (2) the flushing test, and (3) the detection of Co^{60} in the liver by means of a scintillation counter.

The recovery of Co^{60}-tagged cyanocobalamin in the stools is one of the methods that was first employed for this purpose, and was first described by Heinle and his associates. One administers a standard quantity of cyanocobalamin containing some Co^{60} incorporated in the molecule, and the stools then are collected for a sufficient period to insure recovery of that portion of the dose which was not absorbed. In cases of pernicious anemia, when no intrinsic factor is administered, more than 95 per cent of the administered dose is recovered in the stools; however, in normal persons, or those with pernicious anemia, when adequate quantities of intrinsic factor are administered with the vitamin B_{12}, only 20 to 30 per cent of the administered dose of tagged cyanocobalamin usually is recovered. For the success of this method, it is necessary that the stool collections be complete and that the dose of cyanocobalamin be small, for, as will be seen later, not all of the cyanocobalamin which is taken orally is absorbed.

The use of the flushing test was suggested by Schilling.[14-16] He first administers an oral dose of radio-tagged cyanocobalamin, and two hours later he injects subcutaneously 1000 μg. of nonradioactive cyanocobalamin. This test is based on the knowledge that, after the parenteral administration of large doses of cyanocobalamin, a very large proportion of the dose appears in the urine within the first 36 hours. Thus, it is to be expected that when a large dose is injected shortly after a dose is administered orally, before the orally administered vitamin B_{12} is fixed in some nonmobilizable form in the tissues, the body will not discriminate between that vitamin taken orally and that given parenterally, and thus a

certain proportion of the oral dose will also appear in the urine. This in fact is found to be true. Beginning four to six hours after the oral administration of radio-tagged cyanocobalamin, radioactivity appeared in the urine, and continued to be excreted for at least 20 hours, according to Schilling.

The detection of Co^{60} in the liver by using a scintillation counter at specified points over the liver area has been worked out by Glass, Boyd, Gellin and Stephanson[17] and by Glass, Boyd and Stephanson.[18] These authors studied uptake of Co^{60} by the liver by measuring the radioactivity at various points over the intestines and liver. After oral administration of Co^{60}-labeled cyanocobalamin the background count over the intestinal area is greater than that over the liver area, but as the unabsorbed Co^{60}-labeled cyanocobalamin is eliminated in the stools, the background count of areas over the intestine diminishes, and, when intrinsic factor is present, the count over the liver area emerges above the background count of the intestinal area to a significant degree. Thus, the falling count of the intestinal area and the rising count over the liver area serve as an indication of the intrinsic factor activity. In cases of pernicious anemia in which the intrinsic factor was not administered, Glass and his associates observed that the count over the liver never exceeded that over the intestinal area, and thus there was no evidence of uptake by the liver. On the other hand, in normal persons and in pernicious anemia patients also treated with the intrinsic factor, there was definite evidence of uptake by the liver. In a few instances, when the background count remained high over the intestinal area, and the liver count did not rise, there was a striking drop in the intestinal count after administration of a cathartic.

Of the methods mentioned, the flushing test appears to be the simplest, but all three methods are useful in order to study the absorption of vitamin B_{12}. The first requirement is to show without doubt whether these methods offer a true measure of intrinsic factor activity, so as to avoid the laborious testing of activity of intrinsic factor preparations in patients with relapsed pernicious anemia; and the second is to detect if possible those individuals without obvious pernicious anemia who may also have intrinsic factor deficiency which may lead to vitamin B_{12} deficiency.

At the present time, it appears that these methods do in fact measure intrinsic factor activity, and even now a certain amount of progress is being made to detect this deficiency in various types of individuals. In those in whom defect of vitamin B_{12} absorption has been demonstrated by such methods, there has been some indication that the administration of intrinsic factor with the vitamin B_{12} has led to an increased uptake of vitamin B_{12}. At the Hematological Congress in Paris, Glass[19] said:

". . . our data obtained recently tend to show that intrinsic factor preparations may act as agents promoting vitamin B_{12} absorption not only in pernicious anemia but also in other conditions mentioned above (such as chronic alcoholism, chronic gastritis, partial gastric resection, total gastric resection, etc.) associated with defective intestinal absorption of vitamin B_{12}. In younger groups of individuals and to a lesser extent also in some of the selected elderly patients we improved the defective absorption of vitamin B_{12} by adding to vitamin B_{12} a potent intrinsic factor concentrate. This increase in the absorption of B_{12} after addition of intrinsic factor concentrate was statistically significant, with a 'p' value below 0.05.

". . . It may be concluded from these observations that intrinsic factor preparations will find their application also besides pernicious anemia in some selected cases in whom the defective secretion of intrinsic factor results in defective absorption of vitamin B_{12}. From the abundant evidence available it is highly probable that defective intestinal absorption of vitamin B_{12} may result in some subclinical pathological conditions, the clinical symptomatology of which we have yet to learn.

". . . The administration of potent intrinsic factor preparations might be indicated in some of these instances in order to correct the underlying defect in absorption. This may greatly enlarge the scope of applications of intrin-

sic factor preparations in nutrition and clinic in the future."

One awaits with much interest the outcome of the continued studies by Glass and by other investigators who are attacking this problem.

Another approach to this problem has been employed by Chow[20] and by Yomamoto and Chow[21] at Johns Hopkins. These investigators have reported that studies on the fate of vitamin B_{12} administered parenterally or orally to young or old persons revealed a number of age-wise differences; namely: (1) A larger portion of vitamin B_{12} injected by the intramuscular route is retained by the old than by the young; (2) the gastric juice of the old without achlorhydria contained a smaller amount of vitamin B_{12}-binding substances than gastric juice obtained from the young; (3) the mean value of vitamin B_{12} in the serum of the young was significantly higher than that of the old; (4) oral tolerance tests showed that young subjects given orally 1.0 mg. of vitamin B_{12} had a marked elevation in the blood value, whereas only two of seven old subjects showed such an increase. Yomamoto and Chow[21] concluded that these observations are in harmony with the view that certain old persons cannot absorb exogenous vitamin B_{12}, possibly owing to the lack of intrinsic factor, as indicated by the lowering of the vitamin B_{12}-binding substances. These situations result in a lowering of the vitamin B_{12} values in both blood and tissues.

In addition to the hints that intrinsic factor deficiency and, in turn, vitamin B_{12} deficiency may actually exist without obvious pernicious anemia in some patients, these Co^{60}-tracer studies have shown in greater detail what has been touched on earlier in this present report, namely, that even with the intrinsic factor, only a portion of the administered cyanocobalamin is absorbed. For example, when vitamin B_{12} was first available, the daily parenteral dose required to produce and maintain a maximal hematopoietic response was found to be approximately 1 μg.; whereas, the oral dose required to obtain the same effect, even with adequate amounts of active intrinsic factor, was at least 5 μg. per day. The Co^{60} tracer technics have revealed that there is a certain limit to the absorption of oral doses of vitamin B_{12} with intrinsic factor. This has been demonstrated by several, including Swendseid, Gasster and Halsted,[12] by Halsted, Gasster and Drenick,[10] who used the stool recovery technic, and by Glass, Boyd, Gellin and Stephanson,[17] who used the scintillation measurement of the hepatic uptake. Glass, Boyd, Gellin and Stephanson, for example, first showed this tendency when they reported that the hepatic uptake of a single dose of 0.5 μg. of cyanocobalamin, on the average, was normally equivalent to about 0.45 μg. of injected cyanocobalamin, and thus the utilization was about 90 per cent of the dose. After a dose of 1 μg., the average absorption was 78 per cent; with 2 μg., 40 per cent; with 5 μg., 22 per cent; 20 μg., 6 per cent, and with 50 μg., only 3 per cent. Thus a hundredfold increment in the oral intake of vitamin B_{12} resulted only in a threefold increase of the vitamin B_{12} absorbed. Administration of additional amounts of potent intrinsic factor concentrate did not appreciably increase these uptake values.

On the other hand, Baker and Mollin reported at the Hematological Congress in Paris that up to a certain amount of intrinsic factor a stoichiometric relationship exists between the vitamin B_{12} absorbed and the dose of intrinsic factor, but by adding more intrinsic factor a level providing no further absorption of vitamin B_{12} was reached. The cause of this phenomenon was not explained. They also observed that, if they administered a parasympathomimetic drug to stimulate gastric secretion, the amount of vitamin B_{12} absorbed by normal persons was increased. This brings up the possibility that in performing these tests more standardized conditions possibly could be achieved by giving a stimulant so as to produce maximal secretion.

These hints about the limits of absorption of vitamin B_{12} administered by the oral route should be further amplified before one can draw any conclusions, but they can be taken at present to indicate that when patients with pernicious anemia or intrinsic factor deficiency are treated orally, the maintenance therapy should be continued, for it is unlikely that large stores of the vitamin can be laid aside

when the vitamin is administered by the oral route. These studies also indicate that it is unnecessary to administer unduly large amounts of intrinsic factor and vitamin B_{12}, but that reasonable amounts of a reliable preparation are all that is required.

This has been foreseen by the Anti-anemia Board of the U.S. Pharmacopeia, and when they set the standards for the new, official U.S.P. preparation, *Vitamin B_{12} and intrinsic factor concentrate*, the amount of vitamin B_{12} and of intrinsic factor in each U.S.P. oral unit was not overloaded, but was set at that amount which, when given daily by the oral route, will provide adequate treatment for patients with pernicious anemia. Although I know of some cases in which a remission has been successfully maintained for more than 18 months by administering only one-half of a U.S.P. oral unit of an official preparation daily, it is possible that, if stress due to infection should occur, the full dose, or even more, might be required.

It is interesting to note that the official U.S.P. term for the new intrinsic factor concentrate includes vitamin B_{12} and emphasizes the vitamin B_{12} with reference to intrinsic factor which is the natural agent which facilitates the intestinal absorption of vitamin B_{12}. This official stress on vitamin B_{12} in the title places this clearly in the category of another vitamin B_{12} preparation. This preparation obviously provides more certainly for the vitamin B_{12} requirements in all types of cases than a preparation which does not contain the intrinsic factor. With the ever-expanding use of multivitamin preparations, especially in the aged, if folic acid is present in such a preparation, persons with undiagnosed pernicious anemia, or other types of vitamin B_{12} deficiency, would be expected to show an acceleration or exaggeration of nerve lesions, even if the preparation also contained vitamin B_{12}. However, if this vitamin B_{12} were in the form of *Vitamin B_{12} with intrinsic factor concentrate*, the vitamin B_{12} would become available to prevent blood and nerve lesions, except in cases in which disease is unusually resistant.

This review has omitted many interesting recent developments regarding the intrinsic factor, especially the new data on quantities of vitamin B_{12} in the blood, and details of the studies on the nature of the intrinsic factor itself. The goal here, however, has been to describe briefly the present status of the clinical phases of the problem of the intrinsic factor, so that developments as they appear in the near future may be appreciated.

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Bronkephrine in the Management of Bronchial Asthma

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In the treatment of bronchial asthma, epinephrine has always occupied an important place in the armamentarium of the physician. As with most drugs, however, the blessings have not been unmixed. Concomitant with the bronchodilatation have gone certain unpleasant side effects which have precluded its use in many patients. These side effects can be largely avoided by the use of BRONKEPHRINE®,** a sympathomimetic amine similar to epinephrine in its bronchodilating action but markedly different in many other respects. I shall present a short review of the pharmacology of Bronkephrine and a selected number of cases from my own practice which I believe will illustrate these important differences.

Chemically, Bronkephrine is ethylnorepinephrine, 1-(3, 4-dihydroxyphenyl)-2-amino-1-butanol hydrochloride, a compound with chemical properties quite similar to those of epinephrine, but which, from the pharmacologic viewpoint, differs in several important respects. Of these differences, perhaps the lack of pressor action is the most notable. The failure of Bronkephrine to act as a pressor agent was noted and discussed by Tainter, Pedden and James[1] and by Pedden, Tainter and Cameron[2] who investigated the bronchodilator action of a series of sympathomimetic amines and compared them with epinephrine at equibronchodilating doses. This same lack of pressor action has been reported in a study of the clinical effectiveness of ethylnorepinephrine by Bubert and Doenges.[3] These investigators found in a series of 21 cases an average drop in systolic pressure of 7 mm. Hg and in diastolic pressure of 8 mm. Hg 20 minutes following the intramuscular administration of a therapeutic dose. The lack of pressor action exerted by Bronkephrine is of great importance in treating patients in whom hypertension is a problem, particularly in those cases in which there is a question of cardiac asthma. In this last respect Hartman[4] found that ethylnorepinephrine produced no adverse effects in four cases of cardiac asthma, a situation in which an injection of epinephrine could have serious consequences.

Another clinically important difference between Bronkephrine and epinephrine is a general lack of the excitation so often encountered with the use of epinephrine. A significant difference between the central nervous system-stimulating action of these two compounds was demonstrated quantitatively by Schulte and co-workers[5] in animal studies, using an apparatus with which the spontaneous activity of non-narcotized, unrestrained

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**Bronkephrine is the registered trademark of George A. Breon & Company, New York, for its brand of ethylnorepinephrine.

white rats could be measured. These studies indicated an absence of central nervous system-stimulating action by ethylnorepinephrine in doses up to and including fatal ones. In contrast, epinephrine produced a measurable degree of excitation at a level of only one-sixteenth the $L.D._{50}$, increasing to a maximum at half the $L.D._{50}$. Clinical experience, again reported by Bubert and Doenges,[3] indicates the incidence of excitation to be far less than that occurring with epinephrine. This effect, or actually lack of effect, is of real importance, particularly in small children, since such patients, undergoing an attack of bronchial asthma, are already in a high state of apprehension. Freedom from this effect is an important and valuable attribute of Bronkephrine.

Even though Bronkephrine fails to produce the characteristic pressor and excitatory effects of epinephrine, it does provide effective bronchodilatation. This action has been demonstrated by in vitro studies, animal experiments and clinical observations. Tainter et al.,[1] using isolated guinea pig lungs, found ethylnorepinephrine to be an effective bronchodilator, able to overcome completely the effects of various bronchoconstrictors and, in addition, to dilate the bronchi beyond the control values. Studies in dogs by Pedden et al.[2] have led these investigators to rate the bronchodilating activity as moderately strong. On the basis of similar studies, Cameron and Tainter[6] rated ethylnorepinephrine as a good bronchodilator. Clinically it has been found that the degree of bronchodilatation produced by Bronkephrine is as good as that produced by epinephrine, although on a weight basis a higher dosage is required. The following cases illustrate and emphasize the aforementioned advantages of Bronkephrine and, in addition, point out its efficacy and safety in children.

Lack of Excitation

Case 1—H. C., age 3, had been under care for infantile eczema, chronic cough and asthma most of his life. The condition was controlled by small dosages of a tablet containing racephedrine and phenobarbital, but he was brought to the office on June 22, 1954 with a severe attack which had lasted for two days. He was very upset and resisted any examination and, of course, the "needle." Bronkephrine, 0.15 cc., was given intramuscularly at 6:20 P.M., and within a few minutes the child ceased crying and in 15 minutes he calmed down and resumed playing. Subsequent attacks have been infrequent and have been equally well controlled.

Case 2—J. B., age 52, stated that he had asthma first in 1952. He had been under care for weeks in another institution. He was admitted to the United Hospital on May 3, 1954 and was given intravenous and intramuscular aminophylline over a 10 day period. While he had slight relief, on the average it became necessary to give him either epinephrine or aminophylline every six hours. He was given potassium iodide solution, but both of these had to be discontinued because an abscess developed in the gluteal region and a skin eruption resulted from the potassium iodide. Penicillin was then administered. When I took charge of the case on May 14, I discontinued the penicillin and gave Bronkephrine, 0.3 cc., intramuscularly in three doses at 1 P.M., 4 P.M. and 7 P.M. A short steam inhalation was given with each dose. He slept well and was entirely free of asthma the next morning. He has not been admitted to the hospital since.

Case 3—E. M., age 43, had had asthma since 1946 and was treated in the outpatient department of St. John's Riverside Hospital until 1949. Attacks would come prior to menstruation. On repeated occasions Bronkephrine has brought relief whereas epinephrine did not, but caused excitement and cardiac palpitation.

While excitation is rare, the following case illustrates the exception:

Case 4—H. H., age 57, claimed that he first had asthma in 1949. However, examination of x-ray films showed that he had emphysema as early as 1946. He has been in and out of the hospital twice a year or more in the past three years. He attends the outpatient department of St. John's Hospital and none of the physicians there have ever found him clear of rales. On several occasions he has been given Bronkephrine, 0.5 cc., and he always

TABLE 1

CASE	AGE	BLOOD PRESSURE		DOSE	COMMENT
		Before	*After**		
M. B.	50	120/84	115/80	0.5 cc.	Complete relief in 10 minutes
P. M.	43	150/104	150/104	0.3 cc.	Complete relief in 15 minutes
C. S.	59	156/104	142/94	0.3 cc.	Complete relief in 5 minutes
A. T.	23	110/76	106/74	0.3 cc.	Second dose necessary for complete relief
V. L.**	56	134/92	134/92	0.2 cc.	Intravenously, repeated in 20 minutes

*Measured three to seven minutes after medication.
**Case described later in paper.

is relieved of his dyspnea in 20 minutes. There is palpitation and a "jittery" feeling. Objectively, respiration is improved, but he has never been clear of rales.

Lack of Pressor Effect

In table 1, data are presented illustrating the lack of pressor effect of Bronkephrine.

The following cases illustrate the safety and effectiveness of Bronkephrine in children. Cases 5 and 6 are of children who had never had asthma before, and provided a unique opportunity to see the first attacks.

Case 5—C. McD., age 9, had a history of infantile eczema and perennial vasomotor rhinitis, and was referred by a pediatrician. The boy had never had asthma until September 21, 1954, when he was brought in by his mother who could not understand what was happening to him. Bronkephrine, 0.2 cc., was given intramuscularly at 5:05 P.M. He was entirely clear 10 minutes later and has remained well to date.

Case 6—S. G., age 8, had been under care for wheezing at night and cough. The child's mother was certain this was not asthma but only bronchial wheezing! She was brought to the office November 10, 1954, and had a definite attack of asthma. Bronkephrine, 0.15 cc., was given intramuscularly at 4:04 P.M., and complete relief was noted seven minutes later, with no recurrence.

Case 7—P. F., age 8, had infantile eczema and had begun to wheeze two summers ago when at the family cottage in Rhode Island—this building had been closed all winter. She had recovered without medication after a few days on the beach, however. Tests showed sensitivity to grasses and ragweed. She was first seen in the fall of 1953, receiving pollen hyposensitization until leaving for the country in July 1954. She returned home to Rye, New York, in September 1954 and was brought to the office on September 9. Bronkephrine, 0.2 cc., was given at 4:46 P.M. and relief was complete in nine minutes. Subsequently coryza developed and she had some asthma for two weeks in early November. There was some control with racephedrine and phenobarbital. Bronkephrine, 0.3 cc., intramuscularly, was given November 13, at 2:41 P.M., and complete relief was noted at 2:50 P.M.

Case 8—R. C., age 10, at the first visit in December 1951, had a history of asthma in infancy, but now it occurred only in late summer pollen season. Desensitization had been carried out each year. On September 13, 1954, he was brought to the office in the evening, having had severe asthma since that morning. He was given Bronkephrine, 0.2 cc., at 8:43 P.M. and again at 9 P.M. There was complete relief at 9:10 P.M. with no recurrence. It is to be noted that this boy is now 13 and has gained considerable weight. It is my practice to determine whether to use adult dosage in adolescence according to the patient's weight rather than his age.

A great advantage of Bronkephrine is that it is safe to administer intravenously. While intramuscular dosage is usually adequate, oc-

casionally a dramatic result follows intravenous use as in this case.

Case 9—V. L., age 56, when first seen in January 1954, had been admitted to the United Hospital for status asthmaticus. Bronkephrine, 0.3 cc., and sodium phenobarbital, both administered intramuscularly, were given every three hours. After three doses there was complete relief. Hyposensitization to dust was completed in late spring. There was no asthma all summer, but a severe attack developed on November 7, 1954, following coryza. When seen in the hospital the next day she had been in an oxygen tent most of the night and had been given aminophylline intravenously. Bronkephrine, 0.2 cc., was given intravenously at 8:40 A.M. and 9:00 A.M. The result was dramatic and the patient experienced no rise in blood pressure or any other side reaction. The medication was given in an ordinary 2 cc. syringe wherein blood was drawn from the vein to dilute the Bronkephrine, which was then injected slowly. Orders were left that she should receive 0.3 cc. Bronkephrine intramuscularly and LUMINAL® sodium every three hours. Complete relief was noted at 5 P.M. During the several hours since the intravenous injection of Bronkephrine, the oxygen had been discontinued and, in fact, never had to be resumed.

Discussion

It is not uncommon for epinephrine tolerance to develop in the treatment of bronchial asthma. This is particularly true in protracted severe cases where the compound is used too frequently at greater than the minimal dose necessary for effective relief. It is difficult to make an objective statement regarding incidence of refractoriness to Bronkephrine as compared with that to epinephrine without having directed a long-term study toward that end. But, from long personal experience with both compounds, I have seen tolerance develop far less frequently and to a lesser degree with Bronkephrine.

The other points of difference between Bronkephrine and epinephrine, namely, the failure to produce a rise in blood pressure and the lesser degree of excitation produced, have been more amenable to experimental determination. It can be stated that because of these advantages I have found Bronkephrine to be far more than a substitute for epinephrine and am now using it in my practice to the complete exclusion of epinephrine in all cases of bronchial asthma.

Summary

Bronkephrine, a sympathomimetic amine similar in its bronchodilating properties to epinephrine, has been shown to possess several pharmacologic differences which make it a superior tool for the treatment of bronchial asthma. The differences mentioned are:

1. Lack of pressor effect. This was the most marked difference and was found to be of major importance in treating patients in whom hypertension or cardiac disease is a problem.

2. Infrequent excitation. The degree and frequency of excitation were far less than those of epinephrine. This factor was found to be of benefit particularly in the control of asthma in children.

3. Lack of tolerance. The incidence of refractoriness to the use of Bronkephrine was found to be far less than that occurring with epinephrine.

4. Intravenous administration. Bronkephrine can be safely administered intravenously even though the intramuscular route usually provides adequate relief.

The cases described are from private practice and from the outpatient departments of St. John's Riverside Hospital, Yonkers, and United Hospital, Port Chester, New York.

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DIAGNOSTIC CLINIC

Adrenal Insufficiency in Children

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IN 1855, Thomas Addison[1] gave the first accurate clinical and pathologic description of the disease of the suprarenal capsules which bears his name. Subsequent work has increased our knowledge especially as regards the physiologic and the biochemical changes that are associated with this disease.

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Today, three main functions of the suprarenal cortex are recognized: (1) It produces a hormone which regulates the concentration of salt and water in the body; (2) it produces a hormone (S hormone) which regulates carbohydrate metabolism, and (3) it produces a hormone (N hormone) which influences nitrogen metabolism and is closely associated with the production of the secondary sex characters.

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It has not been possible for anatomists and histologists to tell us definitely which part of the adrenal gland is responsible for which function, although it has been suggested that: (1) The zona glomerulosa is associated with the production of the salt- and water-regulating hormone; (2) the middle layer or the zona fasciculata is responsible for the production of the sugar-regulating hormone, and (3) the inner layer, the zona reticularis, produces the nitrogen-regulating hormone, which also is responsible for many of the secondary sex characters. Investigators have suggested that an excess or an alteration of one hormone may interfere with the function of the other hormones.

In the fetus and in the newborn infant, there is a disproportionate enlargement of the suprarenal cortex due largely to a fetal cell layer which later atrophies and disappears. Although the function of this layer is not understood, it may be necessary to protect the infant from the large amounts of various hormones circulating in the mother's blood during pregnancy. Addison's disease represents a loss of all three functions of the suprarenal cortex, and it is characterized histologically by a de-

struction or complete disappearance of the normal architecture of the gland.

Recent work has shown that it is possible for a deficiency of one hormone to occur while the function of the other hormones is apparently normal or overactive. Occasionally, there may be a deficiency of two of the hormones.

Table 1 is a classification of the different types of adrenal insufficiency, based on the histologic changes and functional disturbances. The chronic form of composite or complete renal insufficiency occurs more commonly in adults; it rarely occurs in infants. On the other hand, the acute form of composite insufficiency occurs more often in infants.

Composite or Complete Adrenal Insufficiency

Aplasia—Aplasia of the suprarenal glands has been encountered rarely. It is usually associated with an anencephalic monster or other anomaly not compatible with survival.

Hypoplasia—Hypoplasia of the suprarenal glands usually is observed only at necropsy. In the last two years, a postmortem diagnosis of this condition has been made in four cases at the Hospital for Sick Children in Toronto. In all four cases, the patients were male infants, and they died a few weeks after birth. One of the infants had congenital heart disease, one had coarctation of the aorta, one had multiple congenital defects, and one had cirrhosis of the liver. Electrolyte studies were made in only one of the cases, and the values for the serum electrolytes were normal in this case. What part the suprarenal hypoplasia played in the death of these infants is uncertain; it seems likely, however, that it was a contributing factor.

TABLE 1

ADRENAL INSUFFICIENCY IN INFANCY

COMPOSITE OR COMPLETE INSUFFICIENCY
Aplasia
Hypoplasia
Atrophy
Primary
Secondary
Pituitary disease
Removal of adrenal tumor
Discontinuance of cortisone therapy
Destruction of suprarenal glands
Infection (tuberculosis)
Hemorrhage
Trauma
Hemorrhagic disease
Infection (meningococcemia)
Surgical removal of suprarenal glands
PARTIAL ADRENOCORTICAL INSUFFICIENCY
Deficit in salt- and water-regulating effect
Deficit in sugar-regulating hormone
Deficit in nitrogen (androgenic) hormone

Atrophy—Atrophy of the suprarenal glands may be primary or secondary. The first case of primary suprarenal atrophy was reported by Snelling and Erb[2] in 1935. The patient was a nine and a half year old boy who had all of the typical symptoms of Addison's disease including asthenia, pigmentation of the skin, hypotension and electrolyte depletion. He died in the days when adequate therapy was not available.

Secondary suprarenal atrophy may be caused by pituitary disease, removal of a unilateral suprarenal tumor or discontinuance of cortisone therapy. Craniopharyngioma is a common cause of suprarenal insufficiency, and children who have this disease do not withstand operation very well. In the last three cases in which operation has been performed for this disease at the Hospital for Sick Children, adrenocortical hormone therapy has been used preoperatively, and the children have withstood the operation very well. Presumably, other destructive lesions of the pituitary body also might lead to inadequate adrenal stimulation.

Removal of a unilateral suprarenal tumor may cause sudden collapse owing to adrenal insufficiency. In cases of this type of tumor, the contralateral suprarenal gland is atrophic, since the excessive production of adrenal hormone by the tumor has suppressed the secretion of adrenocorticotropic hormone by the pituitary body. In a recently observed case of carcinoma of the left suprarenal gland, the preoperative administration of cortisone and the postoperative administration of corticotropin (ACTH) and cortisone led to a rapid and uneventful recovery.

Prolonged administration of large doses of cortisone causes suppression of the adrenocorticotropic function of the pituitary body.

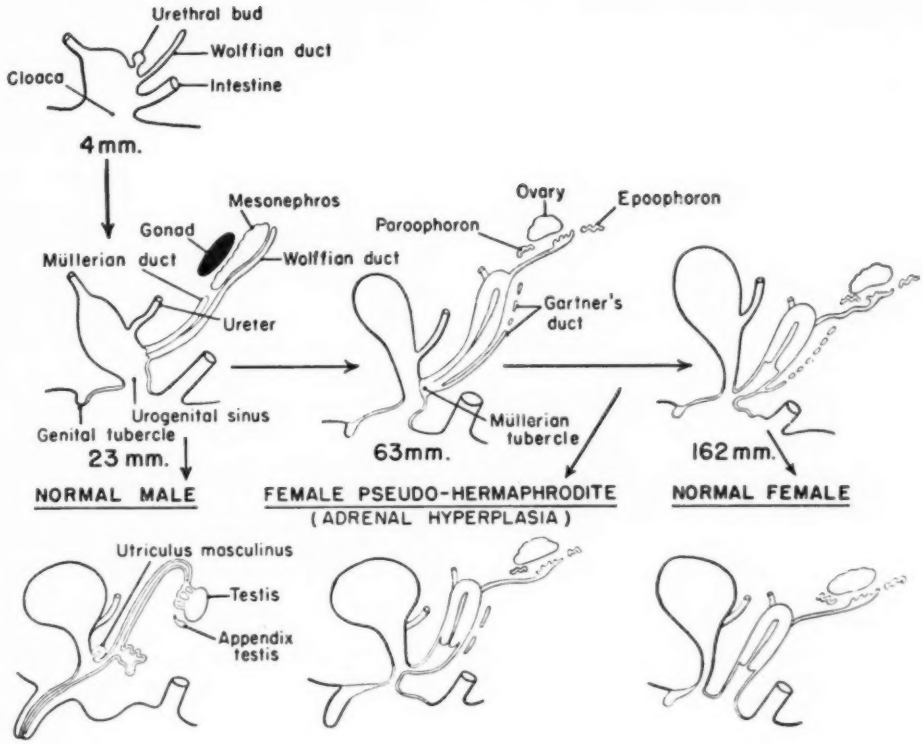

FIGURE 1. Embryologic development of the urogenital sinus. At 23 mm. stage embryo is ambosexual with both müllerian and wolffian ducts. By 63 mm. stage müllerian duct shows complete development in female while wolffian duct has disappeared. Vagina is joined to urogenital sinus by müllerian tubercle which is not yet patent. After this vagina at first communicates with urogenital sinus but with growth of anterior vaginal wall separation of vagina and urethra is completed about stage of 162 mm. embryo. Virilizing effects of congenital adrenal hyperplasia are probably manifested between 63 mm. and 162 mm. stages (12 to 20 weeks).

(From Wilkins, L.: Hyperadrenocorticism. Pediatrics 3:533-544, 1949, with permission of author and editor.)

Stressful situations occurring at various times after discontinuance of cortisone therapy have caused signs of adrenal insufficiency.[3]

Destruction of the suprarenal glands—Destruction of the suprarenal glands may be caused by infection or hemorrhage. Tuberculosis is one of the chief causes of destruction of these glands. It was the only recognized cause of adrenal insufficiency in children until Snelling and Erb[2] reported the first case of suprarenal atrophy. Butler, Ross and Talbot[4] recognized the occurrence of partial and mixed types of adrenal insufficiency in 1939.

Suprarenal hemorrhage may be due to trauma, hemorrhagic disease or infection. Snelling and Erb[5] reported that suprarenal hemorrhage was present in 43 (1.19 per cent) of 3,637 consecutive cases in which necropsy was performed. In 15 of the 43 cases, the patients were newborn infants. In 10 of these 15 cases, the hemorrhage was sufficiently extensive to destroy the structure of one or both of the suprarenal glands.

This condition rarely is recognized before death. Such signs and symptoms as listlessness, vomiting, pallor, dehydration and shock usually are attributed to a difficult delivery, cerebral birth injury or sepsis. If one searches for it, a mass may be felt in the flanks. In some of the cases, the initial symptoms con-

sisted of twitching, convulsions and fever.

In our hospital, we recently have observed a six year old girl who had had hypoglycemic convulsions on two occasions. The first convulsion had occurred in infancy, and the second had occurred a short time before the child was admitted to the hospital. Roentgenographic examination revealed evidence of calcification of both suprarenal glands. The result of a tuberculin test was negative, and roentgenographic examination of the thorax did not disclose any abnormality. The results of tests for adrenal and pituitary function were within normal limits. We strongly suspected, however, that this child had had hemorrhages into her suprarenal glands—possibly at birth—and that she had a greatly reduced adrenal cortical reserve, although no signs of adrenal insufficiency other than the two episodes of hypoglycemia could be demonstrated.

The cause of hemorrhage into the suprarenal glands of newborn infants is obscure. Perhaps hemorrhagic disease or increased vascularity coupled with mild trauma caused by breech delivery may be responsible for the hemorrhage in some cases.

The most fulminating type of adrenal insufficiency is that which is associated with meningococcic infection (Waterhouse-Friderichsen syndrome). Death may supervene within a matter of hours after the onset of the illness owing to complete destruction of the suprarenal glands. Adrenocortical hormone therapy is indicated in all cases of severe meningococcemia.

Surgical removal of the suprarenal glands—Since replacement therapy has become available, surgical removal of both suprarenal glands has been made possible in cases in which this operative procedure is indicated. At our hospital, bilateral subtotal adrenalectomy has been performed on one child with severe Cushing's disease due to bilateral adrenal hyperplasia. Maintenance therapy has been employed postoperatively, and the child is well and free of symptoms two years after the operation.

Partial Adrenal Insufficiency

One of the most interesting chapters in clinical endocrinology has been the recognition of the partial and mixed types of adrenal insufficiency in infancy. Although the composite type of adrenocortical failure usually is fulminating, partial adrenocortical failure usually presents a subacute picture. In the majority of cases, the infant appears well at birth and may appear so for several days or weeks. However, the loss of weight is excessive, and if the nurse is astute she will be impressed with the large amounts of urine passed. At any time, the dehydration caused by renal losses may be aggravated by the onset of vomiting and diarrhea, which rapidly lead to circulatory collapse and shock.

In many cases the vomiting is projectile and is mistakenly ascribed to pyloric stenosis or intestinal obstruction. Frequently, a laparotomy has been performed to the detriment of the patient. In not a few cases, the child has been assumed to be suffering from an infection, and therapy has been directed to this condition. A concomitant infection may be present in some cases, but unless the underlying adrenal insufficiency is treated, it may progress and death may occur in a short time.

In a few cases of adrenal insufficiency, the signs and symptoms indicate that the only abnormality is a deficit in the salt-regulating hormone. It is more common, however, for a deficiency of this hormone to be associated with an overactivity of the nitrogen, or androgenic, hormone. The male infants may have overdeveloped genitalia (macrogenitosomia praecox). The females (pseudohermaphrodites) have an enlarged clitoris, large wrinkled scrotal-like labia, and a urogenital sinus instead of separate urethral and vaginal openings (figure 2). The girls frequently are thought to be boys with hypospadias, but it is easy to establish the true sex by means of skin biopsy since the female sex chromatin can readily be distinguished in the cells of all tissues.

This type of adrenal insufficiency is well illustrated by the following case report.

Case 1—A four week old infant was referred to the surgical clinic for repair of a hypospadias. Since the child obviously was ill, it was transferred to the medical service. Vomiting of varying severity had been present

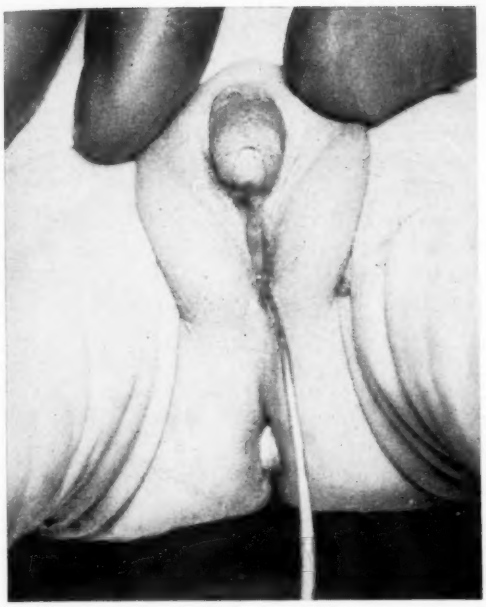

FIGURE 2. Appearance of external genitalia in case of overactivity of the nitrogen or androgenic hormone. This girl, a pseudohermaphrodite, has an enlarged clitoris, large wrinkled scrotal-like labia, and a urogenital sinus instead of separate urethral and vaginal openings.

since birth, and the child had been passing three or four slightly loose stools each day. The child was drowsy. It did not take nourishment well, and it was losing weight.

Physical examination revealed a rather markedly dehydrated infant which in all likelihood was a female pseudohermaphrodite rather than a male infant with hypospadias. The values from the serum electrolytes were as follows: sodium 120, potassium 7.9 and chloride 100 mEq. per liter respectively. The urinary excretion of 17-ketosteroids was 8.5 mg. in 24 hours. One gram of salt was administered orally, and 5 cc. of solution of adrenal cortex extract was administered intravenously every four hours until six doses had been given, and the patient was given a transfusion of blood. This therapy produced a satisfactory response. The child was dismissed from the hospital, and the parents were instructed to give her 1 gm. of salt daily.

The child was readmitted to the hospital three weeks later. At that time, her temperature was 102° F., and she was shocked and dehydrated. The values for the serum electrolytes were as follows: sodium 138 mEq., chloride 103 mEq. and potassium 8.2 mEq. Two grams of salt was administered daily by the oral route, and 0.5 mg. of desoxycorticosterone acetate (DOCA® acetate) was administered daily by the intramuscular route. Two pellets, each containing 75 mg. of desoxycorticosterone acetate, were implanted subcutaneously. The child was dismissed, and the parents again were instructed to give her 1 gm. of salt daily.

The child's condition remained satisfactory for nine months. At that time, nasopharyngitis developed. This was associated with marked listlessness, anorexia and a moderately high temperature. When she was admitted to the hospital for the third time, the values for the sodium, potassium and chloride were 151, 6.0 and 80 mEq. per liter of serum respectively. The glucose tolerance curve was normal. Two more pellets of desoxycorticosterone were implanted subcutaneously. Laparotomy disclosed normal female genitalia and skin biopsy confirmed the sex. The hypertrophied clitoris was removed.

The child now is six and a half years old. She has not required any therapy since she last was dismissed from the hospital, and she has not taken any extra salt. She is tall for her age, and her bony structure is that of a 13 year old child. She has rather marked pigmentation of the skin. The glucose tolerance curve and the values for the serum electrolytes are normal. Cortisone never was administered in this case.

Seven cases of this type of adrenal insufficiency, including the case that I have just reported, have been observed at the Hospital for Sick Children in the past six years. Of the seven patients, four were girls and three were boys. All of the girls were pseudohermaphrodites. In the cases in which the patients were boys, macrogenitosomia praecox either was present at birth or developed subsequently. In two of seven cases, the patients have died. One of these patients was a girl; the other was a boy. The patients in three of the five remaining cases were more than 18 months old when

this paper was written, and they no longer require salt or Doca acetate. All of these patients except the girl in case 1 are receiving suppressive cortisone therapy.

Wilkins[6] reported that there is a synergistic action between Doca acetate and cortisone in cases of adrenal insufficiency. He said that the effective dose of Doca acetate is less when this drug is administered in conjunction with cortisone than it is when the drug is administered alone.

Geppert, Spencer and Richmond[7] were the first authors to report a case of the type of partial adrenocortical insufficiency characterized by a deficit in the sugar-regulating hormone. They also reported some evidence of a deficiency in the salt and water hormone, but there were no signs of intersexuality as there were in case 1. The terminal stage of the illness was ushered in with diarrhea and vomiting which led to convulsions. The values for the blood sugar were very low, the values for the serum sodium and chloride were reduced, but the value for the serum potassium was found to be increased. Although the administration of adrenal cortex extract, the subcutaneous administration of desoxycorticosterone acetate, and the oral and parenteral administration of solutions of salt and sugar previously had been effective, this therapy was ineffective in the terminal stage of the illness. At the time of the patient's death, the value for the blood sugar was 30 mg. per 100 cc. Autopsy revealed hypoplasia of suprarenal glands. The microscopic examination disclosed complete absence of the zona fasciculata and scattered remnants of the zona glomerulosa which were thought to be responsible for preventing an excessive disturbance of the serum electrolytes.

McQuarrie[8] recently reported 25 cases of idiopathic, spontaneously occurring hypoglycemia in which the patients were infants. The urinary excretion of 17-ketosteroids and 11-oxysteroids was normal in all of the cases, and he was unable to demonstrate any evidence of adrenal insufficiency by such means as the epinephrine test or the Thorn test. In all of the cases in which corticotropin (ACTH) was administered, it controlled the hypoglycemia. In some of these cases, it was possible to discontinue the administration of this hormone after variable periods of time without any recurrence of the hypoglycemia. In other cases, it was possible to maintain the patients in an essentially normal state by the administration of reduced doses.

In view of the fact that special tests did not disclose any evidence of hyperinsulinism, liver disease, adrenal disease or other pathologic conditions which might be responsible for the low value for the blood sugar, McQuarrie indicated that the cause of the hypoglycemia in these cases was still unknown. One must agree with this statement, but one cannot help but note that there apparently is a functional type of adrenal insufficiency which may be due to the production of inadequate amounts of the S hormone and which can be corrected by the administration of ACTH. The existence of this type of functional adrenal insufficiency is suggested by McQuarrie's statement that very much larger doses of cortisone or hydrocortisone were necessary to control the hypoglycemia in the cases in which this hormone was used. In this type of functional adrenal insufficiency, there is an excessive need for 11-oxysteroids.

Circumstantial evidence for the existence of this type of functional adrenal insufficiency in infancy is the fact that, like the type of adrenal insufficiency due to a deficit of the salt and water hormone, it has a strong familial incidence and it frequently disappears after a period of supportive therapy. The suprarenal cortex undergoes a marked change after birth. This change may interfere with the function of the gland during early infancy, but the function later may become normal. In early infancy, the urinary excretion of 11-oxysteroids normally is about 0.1 mg. in 24 hours. It is difficult to detect a reduction in the excretion of these steroids by chemical analysis. Biologic assay is the only specific test for the excretion of these steroids.

Some of the cases reported by McQuarrie possibly might be regarded as cases of insufficiency of the S hormone. That this is a very serious condition is borne out by McQuarrie's statement that it may cause serious cerebral

damage. At our hospital, we have observed three cases similar to the cases reported by McQuarrie. The following case report will illustrate this type of adrenal insufficiency.

Case 2—A nine month girl had been normal until she was four months old. At that time, she had begun to have staring spells which had been suggestive of petit mal. In a few weeks, these were followed by frank convulsions and the child was hospitalized.

An electro-encephalogram disclosed diffuse changes. Air encephalogram showed cortical atrophy. The fasting blood sugar (true blood sugar) was only 25 mg. per 100 cc. When a glucose tolerance test was performed, the concentration of blood sugar rose from a fasting value of 25 mg. to a peak of 90 mg., and then dropped to 20 mg. in two hours. Epinephrine caused a normal glycemic response. The value for the blood sugar rose to 160 mg. per 100 cc. but fell rapidly to a low fasting value. A test at the Banting Institute revealed that the blood contained a normal amount of insulin.

Because of the seriousness of the symptoms, 65 per cent of the pancreas was removed. Neither biologic assay nor histologic examination of the excised portion of the pancreas showed any evidence of an excessive production of insulin. The symptoms recurred promptly, and an additional portion of the pancreas was removed. The portion of the pancreas which remained was about the size of a peanut. Biologic assay and histologic examination did not reveal any evidence of an increased production of insulin.

At the present time, this type of adrenal insufficiency is best treated by the administration of long-acting ACTH.

I do not know of any reported case of adrenal insufficiency in which a deficit of the androgenic or N hormone occurred alone in an infant or adult. It seems reasonable to assume, however, that this type of insufficiency might occur and that it probably will be detected with increased knowledge and more careful examination.

I shall briefly outline the treatment of adrenal insufficiency that we are now using at our hospital.

Treatment of Acute Composite Adrenal Insufficiency

Initially, 15 to 25 cc. of solution of adrenal cortex extract is administered intravenously. Thereafter, 10 to 20 cc. of this solution is given intramuscularly every four hours until the immediate danger has passed.

An intravenous infusion of 5 per cent dextrose in physiologic saline solution is started immediately, and 75 to 100 cc. per pound of body weight is administered in 24 hours.

One hundred milligrams of cortisone is administered immediately by the intramuscular route, and a daily dose of 25 mg. is given subsequently. If the child is not vomiting and can swallow, 25 mg. of cortisone may be given orally three times a day instead of administering the drug intramuscularly.

When HYDROCORTONE® is used 25 to 50 mg. of this drug should be administered intravenously.

If symptoms are prolonged, Doca acetate may be used in the same manner as it is in the treatment of partial adrenal insufficiency.

Treatment of (Subacute) Partial Adrenal Insufficiency

Salt-losing type—From 1 to 3 gm. of salt is given daily by mouth. If hydration is difficult to obtain, this is supplemented by the subcutaneous or intravenous administration of physiologic saline solution.

Solution of Doca acetate in oil is given intramuscularly daily. The initial dose (0.1 cc.) contains 0.5 mg. of Doca acetate. This dose is administered every two days until the electrolyte balance is restored without evidence of hypertension or edema.

Pellets of desoxycorticosterone acetate are then implanted subcutaneously. Each pellet contains 75 mg. of the drug. One pellet is implanted for each 0.5 mg. of Doca acetate that is required. If edema should develop or if the blood pressure should increase after the pellets of desoxycorticosterone acetate have been implanted, the daily dose of salt should be reduced in order to re-establish equilibrium. If the value for the serum electrolytes drops, the dose of salt should be increased by 1 or 2 gm. In some cases, one or two addi-

tional pellets of desoxycorticosterone acetate may have to be implanted.

Mixed type with excess of androgenic hormone—If the urinary excretion of ketosteroids is high and if masculinization is prominent, the intramuscular administration of 15 to 25 mg. of cortisone every two days may suppress the overactivity of the suprarenal glands by depressing the production of adrenocorticotropic hormone by the pituitary body. Most children prefer to take 50 to 75 mg. of cortisone per day by mouth.

Low blood sugar type—In cases of idiopathic hypoglycemia, 10 to 15 mg. of ACTH, intravenously, or 50 mg. of cortisone, orally, may be administered daily. If long-acting ACTH is used, the administration of 15 mg. every two days may be adequate.

Prognosis

In cases of partial adrenal insufficiency, treatment should be continued for one or two years. At the end of this period, the patients may regain a reasonable degree of adrenal function. In a few of the reported cases, prolonged therapy has been necessary. It would appear to be the better part of wisdom to use replacement therapy in cases in which stressful situations occur.

Conclusion

As a result of pathologic studies and more accurate biochemical analyses, physicians are beginning to recognize adrenal insufficiency as an important and not uncommon complication in newborn infants as well as in older infants and children.

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Postgraduate Clinical NOTES

39. MENTALLY NORMAL

. . . in what does our "normality" consist? . . . the normality of the normal, from the standpoint of mental health, does not consist in complete immunity, but in relative resilience; . . . we all have some moments of aberration, from which some of us right ourselves more promptly than do others. Recovery is fortunately pretty prompt for most of us. Touches of morbidity, like touches of genius, make the whole of mankind akin, and give us all at least a fleeting share in the whole range of potential human experience.

I discover in my daily work that there are many persons going about their regular tasks pretty effectively, and leading fairly gratifying lives, who harbor, nevertheless, some haunting dread of going crazy. If they only knew how many times they have been there already—and come back, it would be logically expectable that they would lose some of the apprehension.

John C. Whitehorn, *Bulletin of the New York Academy of Medicine*, August 1954, p. 601

Differential Diagnosis of Jaundice

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THERE are three general kinds of jaundice: (1) hemolytic, due to abnormal destruction of red blood cells so that all the pigment cannot be removed from the blood stream; (2) hepatogenic or hepatocellular, in which the liver cells are diseased and cannot completely remove all biliary pigment; (3) obstructive jaundice due to reabsorption of the bile pigment after it has been discharged into the biliary tree.

Hemolytic jaundice usually is easily recognized and does not present difficulty in differential diagnosis. Therefore, I will not consider it further in this discussion.

Hepatogenic jaundice and certain types of obstructive jaundice may mimic one another so closely that differentiation may be quite difficult. It is very important to distinguish between the two, because patients with hepatogenic jaundice should not be operated on (actually, operation might be detrimental), whereas most patients with obstructive jaundice will require operation. Therefore, distinguishing between hepatogenic jaundice and obstructive jaundice constitutes the differentiation of surgical and nonsurgical jaundice.

History and Physical Examination

Taking a careful history is the first step in making this differential diagnosis. Certain types of obstructive jaundice may be diagnosed almost from the history alone. For example, if a patient has intermittent pain, fever, jaundice, chills, etc., one can almost make the diagnosis of stone in the common duct over the telephone. Physical examination is helpful at times, particularly if you are able to palpate an enlarged, nontender gallbladder projecting downward from the surface of the liver in a patient with progressive painless

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jaundice. This is the classic picture of obstructive jaundice due to a tumor of the head of the pancreas.

Liver Function Tests

We speak of the results of the liver function tests as the liver profile. There are a great many liver function tests, some of which are more helpful than others. I should like to tell you about the ones that I feel are important.

First is the determination of the serum bilirubin, the quantitative van den Bergh. The results are expressed in milligrams per cent, as the direct and the indirect reaction. The direct reaction is supposed to be caused by the bile which has gone through the liver cells and been reabsorbed, and therefore represents the part of the pigment that is due to obstructive jaundice. The indirect reaction is supposed to represent that part of the biliary pigment which is due to hepatogenic disease. There is reasonable doubt as to the validity of these assumptions. Nevertheless, the finding of a large preponderance of direct reaction over indirect reaction, for instance, should make one think in terms of obstructive jaundice.

Then there is a group of flocculation and turbidity tests—cephalin flocculation, thymol flocculation, thymol turbidity and zinc sulfate turbidity. The flocculations are reported as 0, 1+, 2+, 3+, and so forth. The turbidity tests are reported in units. In jaundice of hepatocellular type, all these values tend to rise, whereas they are all zero or low in jaundice not due to hepatic disease.

In direct contrast to the flocculation and turbidity tests, the serum alkaline phosphatase usually rises in obstructive jaundice and remains relatively low in hepatogenic jaundice. The usual normal limit for serum alkaline phosphatase is about 1 to 4 Bodansky units. In hepatogenic jaundice it may rise to 7, 8, 10 or even slightly higher. In obstructive jaundice, particularly in the presence of high-grade obstruction of long duration, the serum alkaline phosphatase may rise to very high levels—15, 20, even higher than 30. The important thing to remember is that if the flocculation and turbidity tests are low and the serum alkaline phosphatase is high (and we regard 10 as a rather significant level), one should think in terms of obstructive jaundice.

The prothrombin time is always lengthened in patients with marked jaundice; that is, the percentage is decreased depending on whether the value is given in number of seconds or in per cent of normal. There is an important difference in the way the prothrombin time behaves when vitamin K is given. When vitamin K is administered to patients with obstructive jaundice, the prothrombin time usually returns to normal rapidly, while in hepatogenic jaundice, the return to normal may be delayed or may not even occur.

One other test which is of considerable value is the determination of the amount of urobilinogen excreted in the urine. In many cases of jaundice, the importance of this determination is not very evident, but in those in which there is almost complete exclusion of bile from the intestinal tract, the urobilinogen drops to very low levels. The circulation of the urobilinogen is very complicated, and I will not explain it here. But if the urobilinogen in the urine is very low or absent, one thinks of a complete obstructive jaundice, which is usually caused only by tumor of the duct or compression of the lower end of the duct by a tumor of the pancreas.

Biopsy of the Liver

When all these data are assembled, one may find a very clear-cut picture of either obstructive jaundice or hepatogenic jaundice. Unfortunately, every now and then some of the tests seem to point one way and others seem to point another way. In such cases we term the jaundice as a mixed type. For instance, in hepatogenic jaundice the edema of the liver cells may sufficiently compress some of the smaller biliary radicals so that there occurs a certain amount of obstruction of whatever bile is formed. In such a case, obstructive elements are superimposed on the hepatogenic disease. Similarly, in obstructive jaundice, if there is associated ascending cholangitis or infection in the liver, or if the obstruction is of sufficiently long duration, it is easy to see how the liver cells may become damaged and

then there will be evidence of hepatogenic jaundice superimposed on the obstructive type.

When we are in doubt in such cases, we make use of needle biopsy of the liver. Dr. Schiff and his co-workers in our department of medicine have been largely responsible for the trend toward the use of needle biopsy of the liver at our institutions, and we have now performed more than 1000 such examinations. When this procedure is carried out properly, with suitable precautions, I believe it is safe and very helpful. Its value depends on the skill of the pathologist in interpreting these small bits of tissue. Many of the findings in the large group of cases in which we have employed this procedure have been correlated with findings at operation or at autopsy or with clinical progress, and we feel that we can rely very well on the interpretation that we receive from our pathologist.

Use of Biligrafin or Cholografin

A new method of diagnosing jaundice which recently has been introduced and is more or less in the experimental stage is the use of Biligrafin or CHOLOGRAFIN®, which Dr. Cole* discussed. In high-grade jaundice, it is expecting a good deal for this material to appear in the biliary tree. The important thing is that if you use this material and can demonstrate that there is a dilated common duct, you can be sure you are not dealing with hepatogenic jaundice. In jaundice due to hepatic disease, not enough bile is secreted to distend the common duct, and therefore this finding indicates that the jaundice is of the obstructive type.

Causes of Obstruction

When a case of jaundice has been diagnosed as obstructive and not due to hepatogenic disease, this is where the surgeon takes over. Up to this point, the study of the patient is the joint responsibility of the surgeon and the internist, but when the question of obstruction arises, the surgeon more or less has to make any additional decisions because he is responsible for the type of operation to be carried out.

*COLE, W. H.: Stones in the common duct. (Page 422, this issue.)

There are many different causes of obstruction, but they can be collected into three main groups. The first is stone in the common duct, of which there are many variants. Jaundice due to common duct stone usually is painful and intermittent, and it may be associated with chills and fever. The second cause of obstruction is tumor of the gallbladder, biliary ducts or pancreas. These tumors compress the duct, and in general produce a more or less painless progressive jaundice. The third cause of obstruction is stricture of the common duct.

Stricture of the common duct is of three general clinical types. Nearly all patients with common duct stricture have had previous operation or severe intra-abdominal injury, and the jaundice appears some time later. The first type, seen rarely, is represented by a patient who undergoes an operation, who more or less recovers from the surgical procedure, and in whom progressive painless jaundice develops slowly after six or eight weeks. Stricture of the common duct in such an instance can be explained as follows: The common duct was clamped during the operative procedure but was not ligated or divided. As a result, it is able to carry bile until the area which was clamped is replaced by scar tissue. When it begins to constrict, progressive painless jaundice develops.

The second type of stricture of the common duct may appear as an external biliary fistula which persists after an operation on the biliary tract. These patients often do not have jaundice unless the fistula becomes blocked. However, it is important to remember that they may be much more depleted than the patients who have jaundice; not only is the bile not getting into the intestinal tract (and therefore they have a low prothrombin time) but, in addition, they may have marked imbalance of water and electrolytes due to the constant loss of bile.

The third group of patients with stricture usually have been operated on one or more times and have had recurrence of the stricture. Their history is very much like that of the patient with common duct stones—pain, nausea, chills, fever and itching. Often the itching is more prominent than the jaundice.

Reports of Cases

Dr. Kimbrough has collected several patients with jaundice from some of the hospitals here in Minneapolis, and we would like to present two of them. I shall ask Dr. Kimbrough to summarize their clinical records, and then we shall see how they fit into these categories.

DR. KIMBROUGH: The first patient is a 48 year old man who is a patient at Minneapolis General Hospital. He is of German descent, and apparently his history was difficult to obtain because it is not too clear. He had pain in the right upper quadrant and dark urine for three days prior to admission. Physical findings consisted of mild icterus of the skin and sclerae, spider nevi on the shoulders and neck, demonstrable abdominal ascites, and edema of the ankles. The liver was palpable 5 cm. below the right costal margin.

Laboratory studies disclosed a normal prothrombin time and a normal amount of alkaline phosphatase in the serum. Results of other tests were as follows: bilirubin, 0.7 mg. direct, 2.7 total; cephalin-cholesterol flocculation, 3+; thymol turbidity, 20.5; albumin-globulin ratio, 2.63:3.49.

DR. ZINNINGER: This patient is in the middle age group. His prothrombin time, somewhat to my surprise, is normal; his alkaline phosphatase is normal. The results of the van den Bergh test, which shows 2 mg. indirect with only 0.7 mg. direct, would indicate hepatogenic jaundice. The cephalin flocculation of 3+ also indicates a hepatic type of jaundice. The thymol turbidity is 20.5, again in keeping with the diagnosis of hepatogenic jaundice.

I did not mention the albumin-globulin ratio because, being a surgeon, I am interested primarily in the surgical problem of jaundice rather than the medical problem. I also did not say anything about the enlargement and tenderness of the liver, but I think it is quite clear from the history, the physical findings and the laboratory tests (the liver profile) that this case falls in the category of jaundice due to hepatogenic disease.

DR. KIMBROUGH: The second patient is a 70 year old woman who was admitted to the University Hospitals with jaundice, dark urine and gray feces of about three months' duration. She had not had any abdominal complaints prior to that time. Along with the abovementioned symptoms, she had some right upper quadrant distress, occasionally radiating to the back.

Physical examination disclosed only the icterus and a very hard, slightly tender mass in the right upper quadrant of the abdomen. This mass moved on respiration and apparently was continuous with the liver. Laboratory findings included alkaline phosphatase 54.6; serum bilirubin 7 mg. direct, 12 mg. total; BROMSULPHALEIN®, 44 per cent retention in 45 minutes. The prothrombin time was slightly elevated. The amount of urobilinogen excreted in the urine was 0.6 mg. per day. Thymol turbidity and cephalin-cholesterol flocculation tests were within normal limits.

Exploratory laparotomy revealed carcinoma of the gallbladder with obstruction of the common bile duct and metastases to both lobes of the liver.

DR. ZINNINGER: This clearly is a case of obstructive jaundice. The patient is in the age group in which neoplastic disease is frequently found to be the cause of obstruction. Note that her total serum bilirubin was 12, of which 7 mg. was direct and 5 mg. was indirect. This finding fits in with the assumption that this is obstructive jaundice. The alkaline phosphatase is very high, 54.6. I am not very sure about the reported Bromsulphalein retention; usually we do not try to determine this in patients who are as deeply jaundiced as this one. Prothrombin time was moderately depressed, 16.3 seconds, with a control of 13.7.

Of very great significance in this case is the determination of the urobilinogen, which was 0.6 Ehrlich unit. When the level of urobilinogen is 0.5 Ehrlich unit or less, it nearly always means rather high-grade obstruction and usually makes one think in terms of neoplastic disease occluding the ducts.

Both these patients seem to fit into the proper categories as far as the results of laboratory studies are concerned. They are clear-cut cases, one of obstructive jaundice and the other of hepatogenic jaundice.

FIGURE 1. Oblique view of stomach and duodenum in a patient with jaundice due to carcinoma of pancreas. Note pressure defect where the dilated common duct crosses duodenum just beyond duodenal bulb.

Dr. Pack, in his discussion,* described how he is now advising and carrying out surgical treatment in cases of this sort in which the lesion is limited to the right lobe of the liver. Formerly we thought such cases were not very amenable to surgical treatment. He advocates removal not only of the gallbladder but also of the entire right lobe of the liver. This would not, of course, be a feasible procedure in the case just described, that of the woman who has metastases to both lobes of the liver. I think that many surgeons would still hesitate to carry out the procedure recommended by Dr. Pack, but at least it is one of the things that one might offer to some of these patients. In this particular instance, as in many cases of obstruction of the duct due to a neoplasm in the gallbladder, it would be impossible to reach the duct sufficiently high above the obstruction so the jaundice could be relieved.

Roentgenographic Signs

Figure 1 illustrates one of the x-ray signs in diagnosis of tumor of the pancreas. This is a proved case of carcinoma of the pancreas. Note the pressure which is made on the first portion of the duodenum by the dilated common duct passing under it.

Figure 2 shows another proved case of carcinoma of the head of the pancreas. There are two things I would like to point out in this x-ray: (1) the depression in the duodenal bulb which is caused by the large gallbladder; (2) the enlargement of the duodenal loop due to enlargement of the head of the pancreas. Actually, the mucosa of the inner curve of the duodenum was invaded to a certain degree. The patient underwent operation in the days when we still were doing radical operations for carcinoma of the pancreas. We have largely abandoned radical resection for such cases because of the poor long-range results, and Dr. Waltman Walters of the Mayo Clinic and Mr. Digby Chamberlain* of England have reported similar experience.

FIGURE 2. Anteroposterior view of stomach and duodenum in a patient with jaundice due to carcinoma of pancreas. Note pressure defect on upper surface of duodenal bulb produced by distended gallbladder and also widening of duodenal loop and loss of mucosal pattern on inner aspect of descending duodenum.

*PACK, G. T.: Cancer clinic. (To be published.)

*WALTERS, WALTMAN and CHAMBERLAIN, DIGBY: Pancreatic lesions. Postgrad. Med. 18:301-306 (October) 1955.

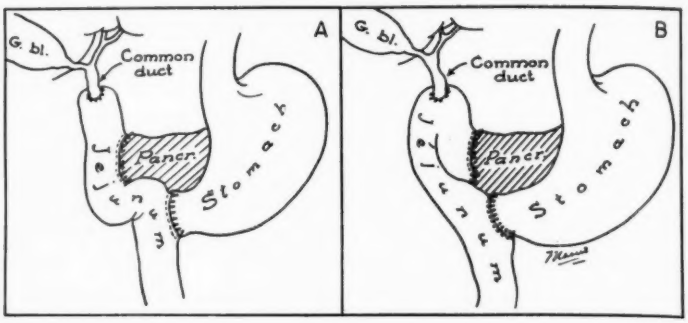

FIGURE 3. Diagrammatic representation of two methods of restoring continuity of common duct, pancreatic duct and stomach to the jejunum after duodenectomy and partial pancreatectomy.

Surgical Procedures

When one does a radical procedure, a modified Whipple operation, we believe it should be done in one stage. Continuity of common duct, pancreatic duct and stomach can be restored by one of the two methods illustrated diagrammatically in figure 3. We believe the entire duodenum should be removed. When you take out the head of the pancreas and remove its blood supply, you also remove the blood supply to all of the duodenum. You then have an open end of the jejunum, and because the common duct often is just about the size of the end of the jejunum you can do a direct end-to-end anastomosis without difficulty. We believe also that it is important to implant the pancreatic duct. It usually is easy to canalize the pancreatic duct because it is dilated. Finally the stomach is sutured distal to these anastomoses so that the peristalsis is all downward from implantation of the bile duct.

A method which is very useful in certain cases when you have a very ill patient is shown in figure 4. The drawings represent its application as a palliative procedure in a case of far-advanced carcinoma of the head of the pancreas. It is helpful if, when one opens the common duct, one makes the incision across the full width of the duct instead of up and down, as it is usually done. Anastomosis to the duodenum is much easier. You place both openings close enough so that you do not have to use a posterior suture line, then run a catgut suture through the mucosa all the way around and then reinforce in front with interrupted Lembert sutures.

Figure 5 shows cholangiograms of a patient in whom this procedure was carried out. He had been operated on once before, at which time a T tube had been placed in the common duct. He had been draining all of his bile through the T tube for several months before I saw him, and figure 5a was made prior to the operation. The procedure I have

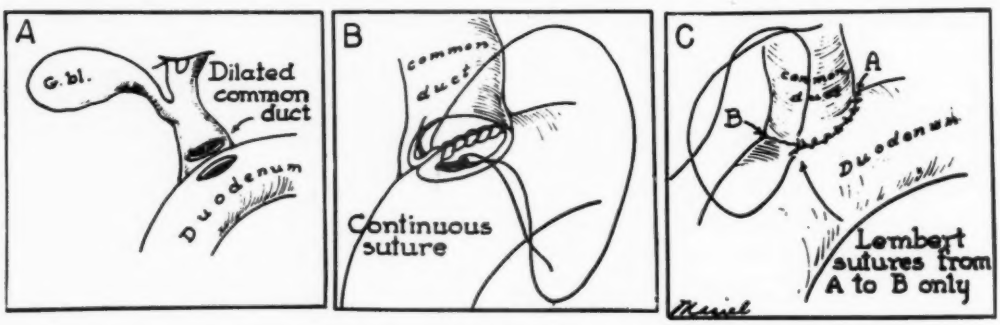

FIGURE 4. Diagrammatic representation of technic of direct anastomosis of dilated common duct to duodenum.

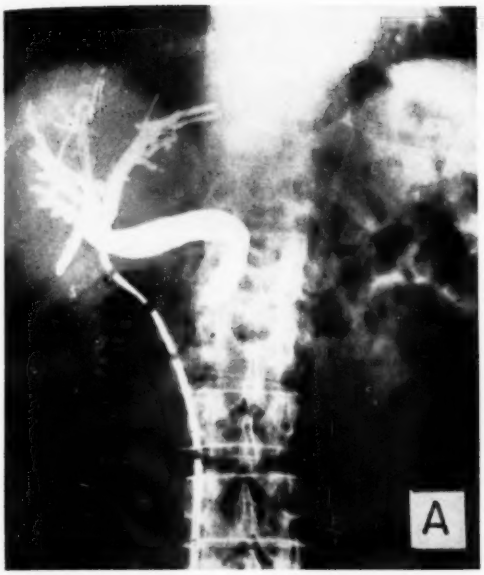

FIGURE 5a. Cholangiogram of patient with obstruction due to carcinoma of pancreas.

FIGURE 5b. Same patient. Barium in stomach six weeks after operation illustrated in figure 4. Barium enters biliary tree, but dilatation of biliary radicals has disappeared. No clinical evidence of ascending infection.

described was done, and figure 5b is a cholangiogram made six weeks later. The barium goes up into the biliary tree, but the radicals are no longer dilated. A direct opening into the duodenum of this sort generally does not result in much difficulty with ascending infection as long as the opening is sufficiently large and remains patent. It is therefore an acceptable procedure.

Figure 6 illustrates the findings in a case of external biliary fistula. The patient came to the hospital following an operation on the biliary tract. The gallbladder had not been removed; it apparently had been drained. The common duct, the hepatic duct, and the level of the stricture in the common duct which was found at operation can be seen in figure 6. This patient was operated on in the days before antibiotics and before we knew about vitamin K. He bled after operation, and with repeated blood transfusions the bleeding finally stopped. Pneumonia then developed, from which he died. The operation was a success locally, but the patient did not recover.

FIGURE 6. LIPIODOL® injection into external biliary fistula. View shows gallbladder, dilated common and hepatic ducts with complete occlusion of lower end of common duct.

DIAGNOSTIC CLINIC

Painful Feet

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THERE are many causes of painful feet, but this discussion will be confined to one very common cause—flatfoot or, more technically, the pronated foot. I like to call it a foot that has a forefoot abduction, and subsequently I shall discuss how and why I have come to that conclusion.

The foot consists of two parts, the rear foot and the forefoot. The rear foot has a large, massive bone called the os calcis, made so because of the great amount of pounding which occurs with each step that a person takes. Because of such usage this bone has become large and thick for its small size, whereas in equinus-footed animals, whose heels are always raised, the os calcis is a small, thin bone. In other words, I want to emphasize that usage is very important to optimal functioning of any part of the body.

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Presented before the thirty-ninth annual Assembly of the Interstate Postgraduate Medical Association at Minneapolis.

The forefoot is the take-off point which ends in the toes. If the toes are used adequately and properly, there will be good take-off of the foot; but if the toes are so cramped that they cannot function well, a good take-off is impossible.

The coming-together, or combination of the forefoot and the rear foot, creates the longitudinal arch, the only function of which is to house such essential structures as the blood vessels, muscles and nerves. The height of the arch is not significant, except that it should be high enough to protect and house those essential structures.

Connecting the forefoot with the rear foot is a very heavy, fibrous tissue called the plantar fascia. It is interesting to note that the junction between the rear foot and the forefoot is always one-third the distance from the tip of the heel to the tip of the great toe. This fact becomes significant when used to record the foot. The junction between the forefoot and the rear foot has a rounded circular joint.

It is the only joint in the foot that allows great range of motion between the forefoot and the rear foot and permits either adduction or abduction of the forefoot. Abduction results in stretching of the plantar fascia which eventually becomes painful. If the body weight is increased or if the integrity of the plantar fascia is decreased, by inheritance or poor nutritional intake, the plantar fascia will stretch and allow abduction of the forefoot. When that occurs, weight thrust of the body downward will come on the inner side of the foot where the soft tissues undergo the stress of weight-bearing. However, if the forefoot is adducted, the weight will be directed to the outer side of the foot where the bones make contact with the floor. Bones thrive under weight thrust. Therefore, it is quite important that the forefoot be held in adduction, or at least in midline with the heel, and not in abduction, which stretches the plantar fascia.

Another factor which militates against good foot posture is the contracture of posterior structures, the calf muscle and tendons. During infancy, we demonstrate an equinus foot structure, as evidenced by a baby's first attempts to walk. For several hours, or even days, he walks on his toes, until he realizes that he is now a biped. From that minute on his heel cord continues to stretch, providing we do not add a heel to his shoe. If the cord does shorten, the foot cannot come down flat, with the weight distributed from the os calcis to the ends of the toes, and the tibia, upright and perpendicular, leans backward. When that occurs, either the heel rises early in the forward step or the plantar fascia gives, and the forefoot becomes abducted. Therefore, it is essential to learn how to adduct the foot, not only by proper exercise, but also by stretching the posterior structures.

Contractures will re-occur if the posterior structures remain unused and unstretched. This is particularly true of children in whom the tibia continues to grow and to increase the length of the leg. The soft tissues, having no propensity for lengthening, will not keep up in length with the tibia unless they are stretched continually.

If we change the foot mechanism from what was intended for it, we will revert to the old difficulties—talipes equinus and stretching of the plantar fascia, allowing the forefoot to abduct. If the plantar fascia is strong and does not allow the forefoot to abduct, there will be increased weight thrust on the metatarsal heads, resulting in metatarsal calluses.

As soon as a heel is put on a shoe, the toes automatically elevate dorsally to come down in a level position. Dorsiflexion of the toes stretches the little flexor muscles in the underpart of the foot and prevents their utilizing the blood supply adequately. This, in turn, initiates degeneration of soft tissues and cartilage about the joints, with resultant pain.

The feet of a 12 year old boy are shown in figure 1. From the rear, one foot deviates medially more than the opposite foot. The medial deviation of the left foot is greater when seen from the front. The varus position

FIGURE 1. Feet of 12 year old boy with medial deviation.

FIGURE 2. Boy's feet in varus position.

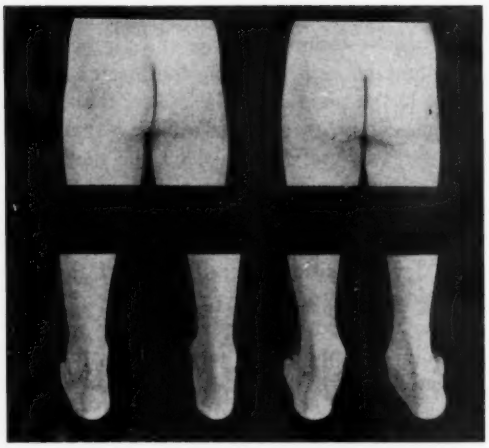

FIGURE 3. Level of buttocks of boy in figure 2.

FIGURE 4. Testing the shortness of the heel cord.

of the feet is illustrated in figure 2. Although the heel is in varus position, the forefoot is not in valgus position because of a rotatory contracture. In such cases, patients are taught to throw the forefoot back into valgus position if the heel is in varus position.

Figure 3 shows the level of buttocks of the same boy. When the feet are protected so that the weight thrust is not on the inner side of the foot, stretching the plantar fascia, the left buttock is higher. On the longer-legged side there is greater relative shortening of the heel cord and a greater amount of pronation, indicating the significance of a short heel cord. If that posterior structure is stretched and kept in this position, protecting the weight stress on the inner side of the foot, the boy's foot position will be improved.

Seventy per cent of people have a discrepancy of leg length. Frequently, a person turns his foot out on his long-leg side as he walks, provided that he has not stretched his heel cord. If he has stretched the heel cord, he will be able to put his foot sagittally in front of himself. When he turns his foot out he lessens the functional length of his foot and therefore lessens the stress from the pull of the short heel cord. Such a person can be noticed right away by the way he turns his feet out or in. If he turns one leg out you know, in 90 per cent of the cases, that the leg is somewhat longer on that side. When individuals turn both feet out, both heel cords are short.

Testing the shortness of the heel cord should be done gently to determine the limit of motion in the foot (figure 4). The angle of dorsiflexion of the inverted foot on the left side is greater than on the right. In walking, as the body weight is carried forward with the heel on the floor, the first pull on the calf muscle stimulates the calf to contract and elevates the heel, which in turn either stretches the plantar

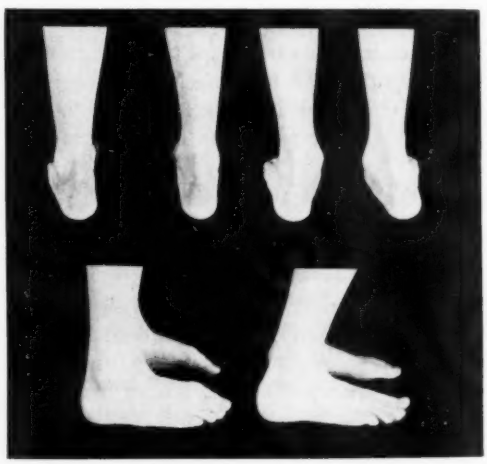

FIGURE 5. Boy standing with feet protected, no weight thrust on the inner side.

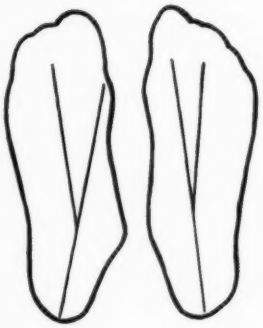

FIGURE 6. Boy's foot tracing showing size and position of astragaloscaphoid junction.

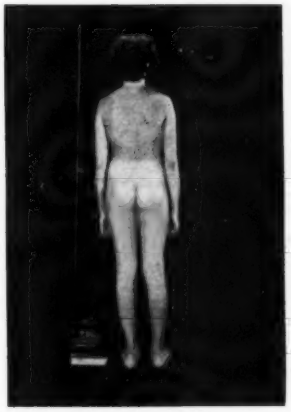

FIGURE 7. Girl with high left buttock, left foot pronation.

fascia or exerts pressure on the metatarsal heads.

In figure 5, the boy is standing with his feet protected, with no weight thrust on the inner side. By leaning forward he is able to stretch his heel cord only as far as shown. When his feet are pronated he can lean forward considerably farther. In other words, with the feet pronated in this position he is not stretching his heel cord but is stretching the plantar fascia.

A line drawn around the foot with the pencil perpendicular to the paper reflects the weight-bearing mechanism on the flat surface. Figure 6 shows the astragaloscaphoid junction, which is greater on the left side. The astragaloscaphoid junction is at one-third the distance from the tip of the heel to the end of the big toe. This joint has a rounded, trochlear surface which has a great range of motion, allowing the movement of the forefoot on the rear foot. At the junction, the outline of the foot is bisected and dotted at the center of the midline of the heel. The same procedure is accomplished at the center of the midline of the forefoot, at the level of the metatarsal heads. Lines connecting these dots form an angle which measures the abduction of the forefoot. On the right side the angle of abduction is much less than it is on the left.

The girl in figure 7 has the high buttock on the left side, with her left foot pronating medially. Figure 8 is a tracing of her feet, with the abduction greater on the left than on the right. It is interesting to note that her left

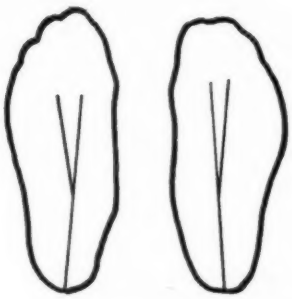

FIGURE 8. Foot tracing of same girl showing greater left side abduction.

leg is longer than her right leg. This discrepancy in leg length is inherited.

Foot tracings are helpful in evaluating foot problems and for determining progress when treatment is started.

We often wonder what happens to people who have not worn shoes. Do they have flat feet? Typical foot tracings of Indians who do not wear shoes reveal interesting side lights on this question. For instance, a foot tracing of a Peruvian Indian who walks over mountains carrying heavy packs shows a broad foot, an angle of adduction, no abduction of the forefoot, and body weight on the outer side of the foot. A foot tracing of a Navajo Indian is

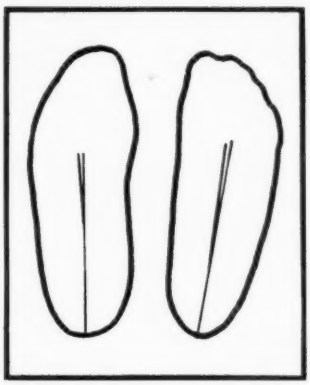

FIGURE 9. Foot tracing of broad-footed Negro man.

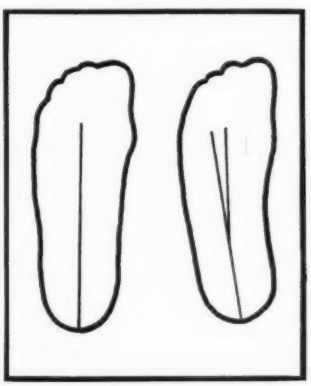

FIGURE 10. Foot tracing of normal white man.

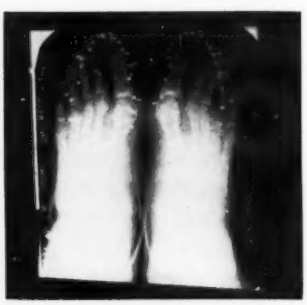

FIGURE 11. Roentgenogram showing toes crowded to center of shoe.

FIGURE 12. Roentgenogram showing well-fitted shoe.

slightly different. He probably rides a horse and doesn't walk over mountains. His tracing shows feet that are not quite so broad as those of the Peruvian, but he, too, bears weight on the outer sides of his feet. Foot tracings of Mexican Indians, who wear a flat, open-type shoe called a *huarache*, also show broad feet and adduction of the forefoot. Figure 9 is the foot tracing of a Negro man. He has broad feet, but he still has an adduction of the forefoot and weight thrust on the outer side of the foot. People like these I have mentioned may have broad feet due to a great deal of weight-bearing, but they do not have pain in their feet, because they do not stretch the plantar fascia.

Figure 10 is the foot tracing of a normal white man who in a natural standing position has the midline of heel and forefoot in a straight line. In the corrected position he adducts the forefoot.

Roentgenograms of feet in shoes can also reveal considerable information. Often by examining such roentgenograms, you can determine how the fit of the shoe relates to various foot problems.

Figure 11 is a roentgenogram showing the toes crowded to the center of the long central part of the shoe. The big toe slides forward into the end of the shoe, separating the heads of the first and second metatarsals, allowing pressure on the medial side of the head of the first metatarsal, which results in skin calluses, fibrous tissue and actual deposition of bone.

Similar roentgenograms can show how too-narrow shoes cramp the toes, resulting in calluses on the dorsa of the toes, which can lead to hammer toes; or, how shoes that are fitted long—but not quite long enough—do not accommodate a foot in all its activity as a person shifts position and goes from abduction to adduction of the foot by turning the body from one side to the other.

A well-fitted shoe, such as the one in figure 12, has adequate space above the big toe, where the big toe belongs, and adequate space on the outer side for the toes to elongate.

The shoe correction for pronation or abduction of the forefoot should put the heel in varus position. This is accomplished by sup-

porting astragaloscaphoid deviation at the forward, inner corner of the heel. The lift height should be adequate—an average of ⅜ to ½ in.—although it may be as much as ¾ in., depending on the severity of the angle of abduction of the forefoot as indicated by the tracing. The forward inner corner rise on the heel should be one-third the length of the foot, as measured on the tracing at the level of the astragaloscaphoid joint. Since the outer counterpart of this joint, the calcaneocuboid joint, is about ½ in. behind the astragaloscaphoid joint, the heel on the shoe is cut back ½ in. on the outer side. With the shank of the shoe flexible, the shoe will move synchronously with the movement of the foot at this midtarsal joint. With weight-bearing, the flexible shank causes the forefoot to go into valgus position, and this adducts the forefoot. The body weight is then put on the outer side of the foot where the bones of the foot approximate the floor.

I am aware that these ideas are not prevalent, and that many shoe men and orthopedic specialists may say, "Oh, you can't take care of a foot that way. You always have to stiffen the shoe shank and support it against gravity." I believe you have to educate the foot. You must make the foot flexible and increase its blood supply by local muscle action to keep the foot alive. Therefore, the lift should be placed at the forward, inner corner of the heel, measured as one-third the distance from the tip of the heel to the toe. Then the outer and the posterior sides of the heel are low, the heel cord is stretched and there is a little tension on the peronei, so the forefoot will return to valgus position. The heel in varus position and the forefoot in valgus position create the arch so necessary to protect the plantar fascia from being stretched. In cases where there is not enough weight thrust to create a valgus position of the forefoot, a little lift is put on the outer side of the sole. Adults can't tolerate quite the lift that children can, and so a lift for an adult's shoe is smaller.

Instructions for shoe correction are:

1. Remove present heel.
2. Make shank flexible.
3. The inner length of the heel should be one-third the length of the foot.
4. The outer length of the heel should be ½ in. less.
5. Only the forward inner corner should be raised its required amount, ¼ in., more or less, as determined by the forefoot abduction measured on the foot tracing.

BOOKS RECEIVED

New books received are acknowledged each month. As space permits, books of principal interest to our readers will be reviewed more extensively. Reviews will be found in this issue starting on page A-112 and additional listings on pages A-46, A-60 and 455.

Applied Medical Bibliography for Students. By William Dosite Postell, Medical Librarian and Professor of Medical Bibliography, Louisiana State University School of Medicine, New Orleans. 142 pages, illustrated. 1955, Charles C Thomas, Springfield, Illinois. $4.50.

Peptic Ulcer. Papers presented at the Fourth Pan-American Congress of Gastroenterology, São Paulo, Brazil, 1954. (Special issue.) Original articles are summarized in English. Revista Brasileira de Gastroenterologia. $5.00.

Cancer Cells. By E. V. Cowdry, Director, Wernse Cancer Research Laboratory, Washington University, St. Louis. 677 pages with 137 illustrations. 1955, W. B. Saunders Company, Philadelphia and London. $16.00.

Splenin A in Rheumatic Fever. By Alvin F. Coburn, M.D., Lucile V. Moore, M.D., Judith Wood, M.D. and Mary Roberts, R.N., The Rheumatic Fever Research Institute, Northwestern University Medical School, Chicago. 87 pages, illustrated. 1955, Charles C Thomas, Springfield, Illinois. $3.75.

Polycythemia: Physiology, Diagnosis and Treatment Based on 303 Cases. By John H. Lawrence, M.D., Director, Donner Laboratory, University of California, Berkeley. 136 pages, illustrated. 1955, Grune & Stratton, Inc., New York and London. $5.50.

Office Procedures. By Paul Williamson, M.D. 412 pages, illustrated. 1955, W. B. Saunders Company, Philadelphia and London. $12.50.

Neuroglia, Morphology and Function. By Paul Glees, M.D., University Demonstrator and Lecturer in Physiology, University Laboratory of Physiology, Oxford University, England. 111 pages with 44 illustrations. 1955, Charles C Thomas, Springfield, Illinois. $5.00.

DIAGNOSTIC CLINIC

Stones in the Common Duct

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STONES in the common duct are really complications of cholelithiasis. Stones do not ordinarily form in the common duct; they gravitate to the cystic duct and, if small, may pass into the common duct where they grow and become larger. Few stones are found to have originated in the common duct.

WARREN H. COLE

Incidence

There is a moderate difference of opinion as to the incidence of stones in the common duct. Dr. Cattell of Boston, for example, explored the duct in 45 per cent of a large series of patients and found stones in 16.8 per cent of his entire series. Contrasted to that, Glenn of New York explored the duct in 10.5 per cent and found stones in only 7.2 per cent. In a recent series of cases at Illinois Research Hospital studied by Harridge and Helsby, we explored the duct in 19 per cent of patients having had cholecystectomy for gallbladder disease and found stones in 12 per cent of the entire series.

It is very important to remember that jaundice is not present in all cases; in fact, only about half the patients who have stones in the common duct have jaundice. Also, stones may be found in the presence of acute cholecystitis with or without jaundice (usually without); reports on the incidence in acute cholecystitis vary between 5 and 10 per cent.

Diagnosis

Stones in the common duct are an important cause of symptoms and jaundice after cholecystectomy. Differential diagnosis may be very difficult.

A few features concerning the differential diagnosis of stones in the common duct versus carcinoma of the head of the pancreas deserve

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emphasis. The patient with carcinoma of the head of the pancreas is usually a little older and usually a man, whereas stones in the common duct are more common in women. The onset is rather sudden with severe pain in 80 per cent of cases of stone in the common duct, whereas it is insidious without pain in 80 per cent of cases of carcinoma of the head of the pancreas. Patients with stone in the common duct are likely to have had attacks previously, in contrast to patients with carcinoma of the head of the pancreas who will not have a history of previous attacks of jaundice. Once the stool becomes acholic in a case of carcinoma of the head of the pancreas, it remains so; that is very important in differential diagnosis. Usually the jaundice and acholic stool are intermittent in patients with stones in the common duct.

Distinguishing obstructive jaundice due to stone from hepatogenic jaundice is exceedingly important, because it is a serious mistake to operate on a patient with virus hepatitis. The liver function tests are very valuable in arriving at the correct diagnosis. For example, in obstructive jaundice the thymol turbidity test is under 5, whereas it will be over 5 and up to 25 or 35 in hepatogenic jaundice. The alkaline phosphatase is above 10 with stones and under 10 with virus hepatitis. The results of the cephalin-cholesterol flocculation test are usually negative with stones and positive with virus hepatitis. The plasma proteins are normal in patients with stones but they are apt to be low with a reversal of the albumin-globulin fraction in hepatogenic jaundice. Prothrombin time is normal in patients with stones and often delayed in virus hepatitis.

Stricture of the common duct is often still more difficult to distinguish from stone in the common duct. The pain is of the same type in stricture, and the intermittent obstructive phase is present both in stricture and in common duct stones. Liver function tests are normal in the early stages of both, but it is very important that patients with stricture nearly always have a chill with an attack of jaundice in the early stages, whereas a chill develops only occasionally with jaundice when patients have obstruction due to stone. The liver is of normal size in patients with stone, whereas it is almost always enlarged in patients with stricture, particularly after the first few weeks of the obstruction; that is due largely to the infection which is universal in cases of stricture of the common duct. Leukocytosis is usually present in patients with stricture and only occasionally in patients with stone in the common duct unless there is infection, such as suppurative cholangitis. Most helpful of all is the fact that in patients with stricture, usually there has been a cholecystectomy, and the implications are clear—namely, that most cases of stricture are due to trauma.

Figure 1 is a chart which shows the febrile reaction in a patient who had a stone in the common duct and a complication, namely, suppurative cholangitis. Incidentally, suppurative cholangitis, in my opinion, is distinctly a surgical lesion. It is unfair to the patient to try to treat that condition with antibiotics. The common duct must be drained, as it was here. This patient had penicillin a few days without any effect, but drainage was established at the point indicated. Except for one temperature spike, which I think was a transfusion reaction, the temperature was under 100° F. for the rest of the postoperative convalescence.

Precautions in Operative Technic

One of the most important operative considerations is good exposure, meaning a long incision. One must be careful in palpating the duct lest a stone is forced up into the liver. I did that on one occasion and the stone lodged behind the bifurcation from which location I could not dislodge it. I took it out at a later operation. It is safer to aspirate the common duct before opening it, because there might be an anomaly, or one might open the portal vein or the right branch of the hepatic artery.

If the indications are not clear-cut for opening the common duct, make a cholangiogram while the patient is on the table. I am not a believer in routine cholangiograms on the table, but I do think that now and then they are extremely helpful, particularly if one is not sure about the presence of a stone or about the indications, and I have had cho-

langiograms made on numerous occasions.

Another precaution in exposing the ductal area is to incise the peritoneum and clear the fat off the common duct before making the incision. Remember that the right branch of the hepatic artery lies anterior to the common duct in 15 or 20 per cent of cases; if you do not have the common duct well exposed you might section the right hepatic artery, which is a very serious error. I like to put stay sutures in the wall of the duct to lift it up so when you cut into it you will not cut through and perhaps damage the portal vein beneath.

After removing the stones, you must be sure that the probe will go through the sphincter of Oddi, namely, be sure that the sphincter of Oddi is well open; if it is not, you must open the duodenum and find out why you cannot get the probe through. Sometimes it is very difficult to tell whether or not the probe has passed through the sphincter of Oddi. There is a very simple way to tell: Press the probe up against the wall of the duodenum; if you are looking through only one wall of the duodenum (meaning the probe is inside the lumen) you will actually see the lead color of the probe, but if you are pushing both walls of the duodenum forward you cannot see the lead color. That test practically never fails.

Also, when performing choledochostomy for stones, give a pint of blood as a routine; at least make up the deficit. Get a culture, and at the end of the operation I like to put a T tube in the duct because now and then there is drainage of considerable bile, even though you may suture the duct carefully. Leakage of bile into the free peritoneal cavity can cause death from bile peritonitis unless you recognize the condition promptly and remove the bile by operation. I lost a very good friend of mine, operated on elsewhere, who had his common duct opened and not drained; he died of bile peritonitis.

The indications for opening the common duct are fairly clear-cut. We open it when we feel stones, when the duct is dilated, when the wall is thickened, and often when we aspirate turbid bile with cholesterol deposits in it. Another important indication is obstructive jaundice or a history of obstructive jaundice. However, let me remind you to be sure that the

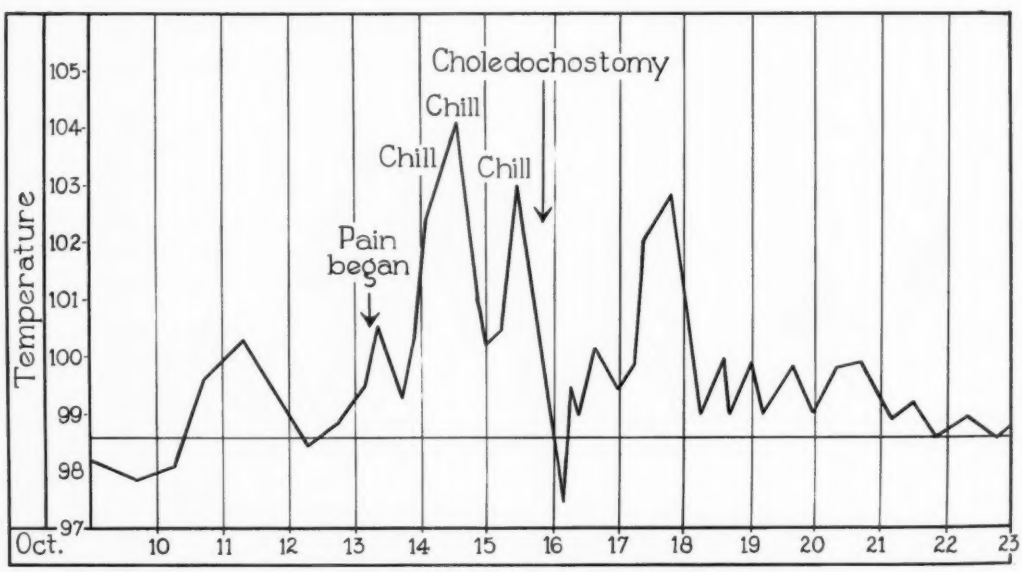

FIGURE 1. Temperature chart of patient with a stone in the common duct and suppurative cholangitis. Favorable response to choledochostomy.

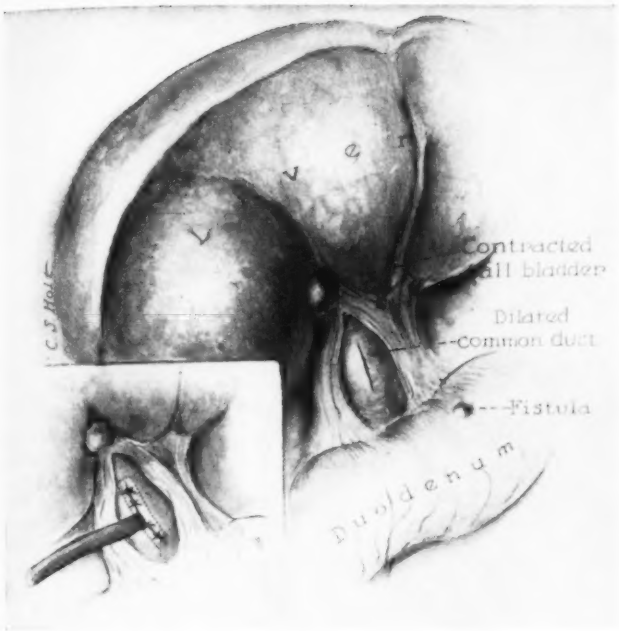

FIGURE 2. We had diagnosed this case as malignancy with hepatic metastases, but a stone in the common duct was found at operation. The patient had had jaundice for more than a year without pain.

jaundice is obstructive in type, because the most common cause of jaundice is virus hepatitis, not obstructive jaundice.

The drawing in figure 2 illustrates a case which taught me a very important lesson. The patient, a 72 year old woman, had been jaundiced for over a year, with no pain. We thought she had metastatic disease of the liver, but we could not find any positive evidence of it. Finally we decided we must not let her go home without confirmation, so we operated. She had a stone in the common duct with a fistula between the gallbladder and duodenum. We opened the common duct and took out a stone, after which she promptly got well. What a serious mistake it would have been to send her home as a terminal case of carcinoma of the liver.

Occasionally you cannot get the stone out through the incision in the duct; if so, you have to open the duodenum and extract it from the sphincter of Oddi side. Sometimes that is fairly easy; sometimes it is very difficult. Occasionally a stone is encysted in the duct and you cannot dislodge it. On four occasions in the past five or six years I have been unable to extract a stone with a common duct scoop, and have crushed it with my fingers. When you crush the stone you can wash it out with saline. This complication, viz., inability to remove palpable stone, does not happen often, but when it does, crushing the stone is an extremely helpful procedure, although it is rather traumatic.

The operative cholangiogram shown in figure 3 is that of a patient who was not jaundiced at the time of operation, but had severe pain with one or two febrile attacks. We could not feel stones in the common duct, largely because of severe acute pancreatitis and considerable edema around the ductal area. There were three shadows indicative of stones, and considerable filling defect which turned out to be bile precipitate; three definite stones were found and removed.

We performed cholecystectomy and choledochotomy on this patient and took a cholangiogram two weeks later before removing the T tube (figure 4). A filling defect quite indicative of stone was seen. This proves the necessity of taking a cholangiogram before removing the T tube placed in the duct following

FIGURE 3. Cholangiogram taken while the patient was on the operating table. Stones were not palpable because of acute pancreatitis and considerable edema about the ductal area, but were shown on the cholangiogram.

choledochotomy. This procedure is a very simple one which will find residual stones with a high degree of accuracy. I usually take the cholangiogram on about the fifteenth day and remove the T tube a day or two later if stones are not found. Obviously the tube should not be removed unless stools are of normal color and the cholangiogram reveals no obstruction. Occasionally, when pancreatitis is present a partial obstruction may remain for several weeks after operation.

The cholangiogram in figure 5 was taken two and one-half months later. The "stone" shadow is no longer present. It had either dissolved or passed. We took the tube out a day or so later and the patient reported no further difficulty when last seen two years later.

Figure 6 is a cholangiogram obtained following intravenous administration of CHOLOGRAFIN®,* which is a benzoic acid derivative. It consists of about 55 per cent iodine, and is now available to the medical profession. You give about 40 cc. of it to the patient and take these pictures 10 to 20 minutes later.

*Made by E. R. Squibb & Sons.

Artefacts are very treacherous. A roentgenogram taken a few minutes after the cholangiogram illustrated in figure 6 shows two or three negative shadows which closely resemble stones (figure 7). Yet when we compare this with the cholangiogram we have to admit that apparently figure 6, which presents such a normal appearance, is probably a correct portrayal of the duct, and the shadows seen in the roentgenogram are artefacts.

We have a couple of patients whom I would like to discuss. Dr. Kimbrough has abstracts of their histories, and x-rays which illustrate certain important points.

DR. KIMBROUGH: The first patient is a 19 year old Indian girl who was completely healthy until three months before admission. Gaseousness and some epigastric distress developed, but the attack was not really typical of gallbladder pain until about 18 hours prior to admission when she had a severe right upper quadrant pain that radiated around the right costal margin. She was seen at another hospital and found to have severe right upper quadrant tenderness and muscle spasm, and

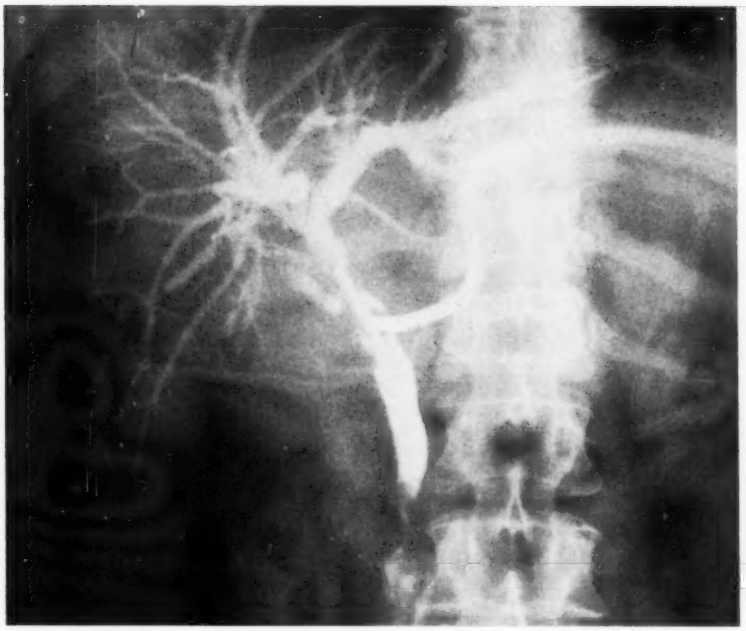

FIGURE 4. Same patient as in figure 3. Cholangiogram taken two weeks after cholecystectomy and choledochotomy, at which time three stones were found in the common duct. The patient was not jaundiced at the time of operation. Note the shadow in the terminal end of the duct which appears definitely to be a stone. (Reproduced courtesy of the *Journal of the American Medical Association.*)

was then referred to the University Hospitals. Abdominal palpation did not disclose any abdominal tenderness, but there was severe tenderness to the right on rectal examination.

Temperature, white cell count, and serum amylase all were normal, but the serum bilirubin was elevated, with a 3.4 total, 1.8 at one minute. She was taken to the operating room immediately, the abdomen was explored, and she was found to have an inflamed, edematous gallbladder containing many small stones. A cholangiogram was made and stones were found; the duct was opened and the stones were removed. Another cholangiogram taken following removal of the stones did not show any suspicious shadows.

DR. COLE: In the cholangiogram taken on the operating table before the common duct was opened, there is a definite defect in the duct shadow which was easy to interpret at the time of operation. This coincides with the clinical picture insofar as the patient was jaundiced and stones were found in the common duct. If stones had not been found in the common duct, two or three other possible ex-

FIGURE 5. Same patient as in figures 3 and 4. Cholangiograms taken after the one shown in figure 4 still disclosed the stone, but this one, taken after two and a half months, no longer shows the stone. Apparently it had passed or dissolved.

FIGURE 6. Cholangiogram in the case of a patient who had pancreatitis of several months' duration. The shadow is comparatively normal, revealing no filling defects.

FIGURE 7. Roentgenogram taken 10 minutes after the cholangiogram in figure 6 was made. Several artefacts resembling stones are seen. Positive conclusions cannot be drawn, but since the shadow in this film is less dense than in the former which presents such a normal appearance, we are inclined to ignore the defects in this film.

planations for the jaundice present themselves. One of them is acute hepatitis secondary to acute cholecystitis; this type of jaundice is rarely intense. Another possible explanation is acute pancreatitis; however, the jaundice encountered in this disease is rarely intense. It is the surgeon's job, of course, to determine the source of the jaundice because he must act accordingly to correct it, if at all possible.

How many stones did you find, Dr. Kimbrough?

DR. KIMBROUGH: One large stone and several small stones in the common duct, and many small stones in the gallbladder.

DR. COLE: And then you took a cholangiogram before you closed the patient's abdomen?

DR. KIMBROUGH: Yes.

DR. COLE: The cholangiogram does not show any stones, implying that you thought you removed them all. Fortunately, any remaining stones too small to show up on a cholangiogram would probably be small enough to pass into the duodenum unless the patient had an anomaly at the sphincter of Oddi in the form of a stenosis; if a stenosis is present, even small ones will not pass, but they may produce symptoms even to the point of causing jaundice.

We have another similar case.

DR. KIMBROUGH: A 44 year old white woman came to the hospital in considerable distress. She was afebrile and had a normal white cell count and was not icteric, either clinically or by clinical tests, but she did have severe tenderness with a mass in the right upper quadrant, of two days' duration. Celiotomy was performed and an acutely inflamed gallbladder with stones in the common duct found. A cholangiogram taken after the stones were removed from the common duct did not show any residual shadows.

DR. COLE: These patients had very similar histories. They had acute cholecystitis. One of them had more acute symptoms than the other, but they were both classified as acute cholecystitis and both of them had evidence of acute inflammation in the gallbladder. Right?

DR. KIMBROUGH: That is right.

DR. COLE: Remember, I remarked earlier

that 5 to 10 per cent of patients with acute cholecystitis have stones in the common duct; only half of those, or perhaps less, will be jaundiced. These points emphasize that when you are operating on patients with acute cholecystitis you must bear in mind the possibility of stones in the common duct, even without jaundice. Except in rare circumstances when the patient's condition is precarious, these stones should be removed at the time of operation for acute cholecystitis, thus sparing the patient a second operation.

Postoperative Precautions

If patients are jaundiced, we continue to give vitamin K for several days to prevent hemorrhage, which can be very serious and even fatal. Also, of course, we determine the prothrombin time in all patients with jaundice; this tells us whether or not the vitamin K deficiency is significant.

The average patient having choledochostomy for stone is really not seriously ill unless he has an acute infection or some other serious complication. Nevertheless, we almost invariably leave a tube in the stomach for 24 hours for decompression. The patient will be much more comfortable if you do so; you can start water by mouth the following day.

There is considerable discussion as to how long a T tube should be left in place. I am much in favor of leaving a tube in no longer than 15 to 18 days; you cannot take it out in three or four days because there are not sufficient adhesions around the tube to prevent extravasation of bile throughout the peritoneal cavity if it leaks out through the duct around the tube. This diffuse collection of bile results in bile peritonitis, a very serious complication which is usually fatal unless celiotomy is performed, the bile removed, and further leakage into the peritoneal cavity prevented. So we like to leave the T tube in the duct until adhesions have formed around the tube, giving a solid tract which will not allow escape of bile into the free peritoneal cavity. It takes about 10 days for that to take place.

As I have already said, there are strong indications for making a cholangiogram with DIODRAST® or a similar product about the fifteenth or eighteenth day before you take the T tube out, to be sure that there are no stones left in the duct. If there are, I am learning that we should not be in too big a hurry to operate on those patients, because often the stones pass or dissolve.

Dr. Best of Omaha has been advising a flushing of the common duct with chloroform and ether, and has reported good results. I have not had much experience with that method so cannot tell you how effective it is.

If the patient having choledochostomy for stone has much evidence of infection, I think we should give antibiotics, particularly since cultures of the bile are almost always positive when stones are present, even though fever may not be present. The advantage of taking a culture at the time you open the common duct is obvious. In a day or so you have the organism identified and if the infection does happen to flare up, which does not occur very often, you will be able to treat that infection very intelligently after you obtain the results of the sensitization test.

Infection in the common duct is usually caused by one of three organisms: *Streptococcus*, *Staphylococcus* and *Escherichia coli*. Sometimes all three are present, and on other occasions only one. Therefore, penicillin and streptomycin represent a pretty good shotgun prescription until you identify the organism and determine its sensitivity.

We have improved our results following choledochostomy for stones largely through the more intelligent use of blood and better postoperative care, as well as through better preoperative care in correcting malnutrition. If a patient with obstruction of the common duct due to stone has so much pain that he has been unable to eat for several days preceding admission, you should not operate on him the next day, because you will have a 15 to 20 per cent mortality rate. If you watch these points, and treat effectively any existing complication, the mortality rate following choledochostomy for stones should be about 3 to 5 per cent. If you fail to correct physical decrements, it will be much higher. Obviously the mortality rate is higher in patients with jaundice than in patients without jaundice.

SCIENTIFIC EXHIBIT

The INITIAL MANAGEMENT of the SEVERELY WOUNDED

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INITIAL HOSPITAL CARE...

As soon as a patient reaches the hospital, the physician must evaluate the patient's over-all condition. Roentgenographic examination and other diagnostic tests are delayed until after instituting restorative therapy. Tetanus antitoxin and a booster dose of toxoid are required. When the barrier against bacteria has been broken, antibiotics should be given to prevent infection; the intravenous method usually is preferred. Oxygen may be given if there is cyanosis or marked deficiency of blood volume. A catheter inserted in the bladder indicates the adequacy of circulation by permitting measurement of the urinary output. In wounds of the abdomen, an indwelling gastric tube decompresses the stomach and aids in preventing aspiration. One of the most important phases of hospital care is the adequacy and speed of blood replacement. Blood must be given at a rapid rate to severely wounded individuals who are quite hypotensive. There appears to be no particular advantage in employing the intra-arterial route. A large-bore needle, a cut-down or a femoral cannula (figure 1) should be used.

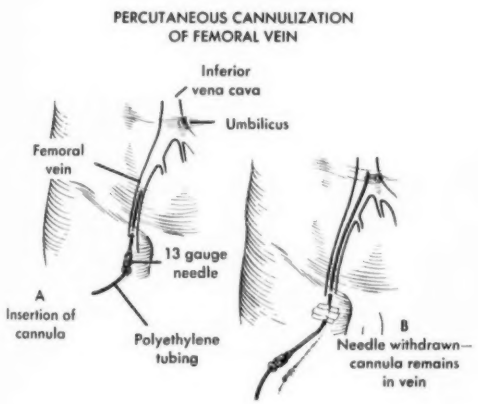


FIGURE 1. **Femoral cannula.** When a suitable vein is not available for a cut-down, a 13 gauge needle may be inserted into the femoral vein. A measured segment of polyethylene tubing is threaded through this needle into the inferior vena cava. The needle is withdrawn, leaving the tube in place. In five to seven days the tubing is removed, thus avoiding formation of thrombosis which might cause pulmonary emboli.

WHEN TO OPERATE...

It is most difficult to tell when a patient is ready for operation. If there is severe, uncontrolled hemorrhage, immediate operation is mandatory for the control of this hemorrhage. On the other hand, if bleeding has been controlled, the patient should be restored to a near normal state before undergoing further trauma of anesthesia and surgery. Adequate resuscitation for operation is achieved when the systolic blood pressure is 110 mm. Hg or above, pulse rate 120 or below, and urinary flow at least 30 cc. per hour.

SURGERY OF THE EXTREMITIES

CASE 1.

A large, avulsive wound of the right forearm was caused by mortar-shell fragments. The arm was splinted at a battalion aid station. Then the patient was evacuated to the forward surgical hospital, arriving approximately one and a half hours after injury. There was a contusion of both the ulnar and median nerves, and an open, comminuted fracture of the radius and ulna extended into the elbow joint. Preoperatively, the patient received 500 cc. of dextran and 500 cc. of blood. The wound was débrided and the patient was evacuated to the rear in good condition.

FIGURE 2a. **Before débridement.** This avulsive wound of the forearm was caused by mortar-shell fragments. There was loss of skin, destruction of muscle, and exposure of nerves and bone.

FIGURE 2b. **After débridement.** The damaged muscle was excised and two sutures were placed in the muscle to cover nerves and exposed bone. Since the joint capsule was destroyed, the skin was approximated to cover nerves and exposed bone. The area was drained. The wound was closed by a skin graft at a later date.

CASE 2.

A 37 year old officer sustained an injury of the right leg caused by accidental discharge of a 30-caliber rifle during a hunting trip in Alaska. A tourniquet, applied immediately to the thigh, remained in place for 12 hours. On arrival at the nearest hospital, the patient's leg was pulseless, cold and without sensation. He was operated on without restoration of blood volume. The sural nerve and posterior tibial artery were lacerated. A minimal débridement was performed. A period of prolonged hypotension followed operation, and norepinephrine and 3000 cc. of blood were administered. Acute post-traumatic renal insufficiency developed, and the patient was transferred to Brooke Army Hospital. On arrival, his potassium was 6.1 mEq. per liter and the blood urea nitrogen was 164 mg. per cent. On exploration, the wound showed extensive muscle necrosis of the anterior and posterior tibial compartments. A below-the-knee amputation was necessary. Two hemodialyses by means of the artificial kidney were required before the onset of diuresis on the twenty-third day following injury. The amputation stump healed without difficulty and the patient recovered.

FIGURE 3a. **Before exploration.** The initial débridement of this high-velocity missile wound was entirely inadequate. The small incision did not permit exposure of deep muscle bundles. The leg was discolored, swollen and tense on the patient's arrival at Brooke Army Hospital.

FIGURE 3b. **Adequate exploration.** A long incision was required to expose the devitalized muscle in the deeper portion of the wound. Soft, mushy muscle failed to react when stimulated. After a thorough examination, no viable muscle was found in the lower leg. It was believed that the dead tissue increased the severity of the renal insufficiency. As a lifesaving measure, the patient's leg was amputated below the knee. Hemodialysis was carried out later by means of the artificial kidney and the patient recovered.

FRACTURE...

CASE 3. A 22 year old soldier sustained multiple mortar-fragment wounds of the left leg and open, comminuted fractures of the tibia and fibula. Hemorrhage was controlled by a firm pressure dressing. This soldier received 500 cc. of dextran at a battalion aid station prior to evacuation by helicopter to the forward surgical hospital, where he arrived two hours after injury. He was given 1000 cc. of blood and taken to the operating room. After thorough débridement, the wounds were dressed and a long leg cast was applied. He was evacuated in good condition.

FIGURE 4a. **Before débridement.** Many small openings in the skin were caused by multiple shell fragments. Although injuries did not appear to be severe, it was necessary to open each wound in order to explore the underlying muscle.

FIGURE 4b. **After débridement.** Long incisions were required for adequate exposure of devitalized muscle. Severe damage existed beneath the skin. The fascia was opened longitudinally in order to expose all dead muscle. Débridement of multiple areas causes loss of large amounts of blood.

FIGURE 4c. **Cast for transportation.** Open, comminuted fractures are splinted by means of a cast which is applied after débridement of the wounds. It is not necessary to reduce the fracture. Every cast is split on one side before a casualty is evacuated. Removal of a ½ in. segment of the cast insures complete division. Before applying sheet wadding, a rubber tube placed next to the skin and later removed assures an adequate opening in the cast.

AMPUTATION...

CASE 4. A 30 year old soldier sustained a traumatic amputation of the left leg when a grenade exploded in his bunker. A tourniquet was applied immediately and left in place until his arrival at the forward surgical hospital. At a battalion aid station, he received 500 cc. of dextran. He received 1000 cc. of blood at the hospital prior to operation. There was extensive destruction of the muscle with laceration of nerves and blood vessels. He had open, comminuted fractures of the tibia and fibula. Amputation was necessary.

FIGURE 5a. **Below-the-knee guillotine amputation.** A guillotine amputation is rapid. Secondary revision can be carried out later.

FIGURE 5b. **Application of skin traction.** The skin proximal to the amputation site is coated with an adhesive agent, and stockinet is applied over the stump. Fine-mesh gauze is placed against the wound and the amputation stump is covered with a large dressing of gauze fluffs.

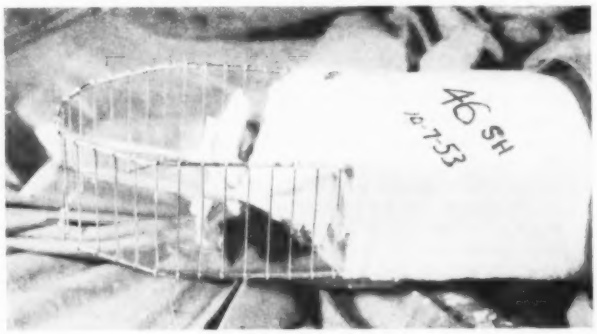


FIGURE 5c. **Use of cast for skin traction during transportation.** A cast with a wire ladder splint is placed on the amputation. The stockinet, attached by a Penrose rubber drain to the wire ladder, provides even, resilient retraction.

VASCULAR INJURIES...

Injuries to major blood vessels frequently lead to amputation unless the continuity of the vessel is restored. All patients having injuries of the extremities should be examined for possible vascular injury. Lacerated arteries bleed profusely, and usually a tourniquet is required to control hemorrhage. When an artery is completely divided, it may retract and form a clot, thus preventing gross hemorrhage. When a major artery is severed, the extremity will be pale and cold. In most instances the peripheral pulse will be absent. There may be decreased sensation and some fixation of the joints.

Completely divided arteries are repaired by end-to-end anastomosis unless the defect is so great that it cannot be approximated without undue tension. In such cases, a vein graft or homologous arterial graft may be used to bridge the defect. If there is a laceration of more than one-third of the circumference, the artery should be completely divided and an end-to-end anastomosis performed. After the blood vessel is repaired, it is covered with surrounding muscle or subcutaneous tissue. Postoperatively, the extremity is kept at the same level as the trunk and covered with a blanket. Heat is not applied. Anticoagulants are not indicated. Fasciotomies may be necessary when there is an extensive swelling of the muscles, with increased tension in the fascial compartments.

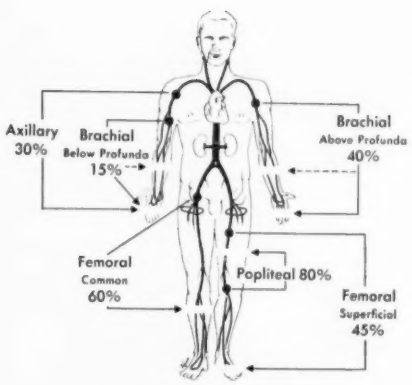


FIGURE 6. **Incidence of amputation after acute interruption of major arteries.** This diagram, prepared from statistics assembled during World War II, points out the expected incidence of amputation after injury to different arteries and emphasizes the need for repair of major vascular channels following acute injury.

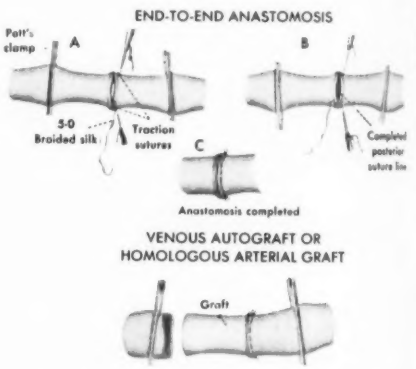


FIGURE 7. **Vascular anastomoses.** A simple end-to-end anastomosis is carried out after trimming the frayed ends of the vessel. Large defects may be bridged by a venous autograft or homologus arterial graft.

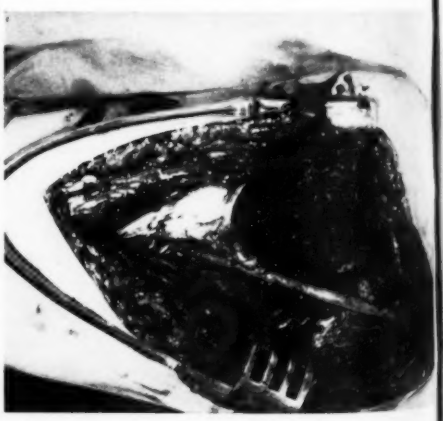
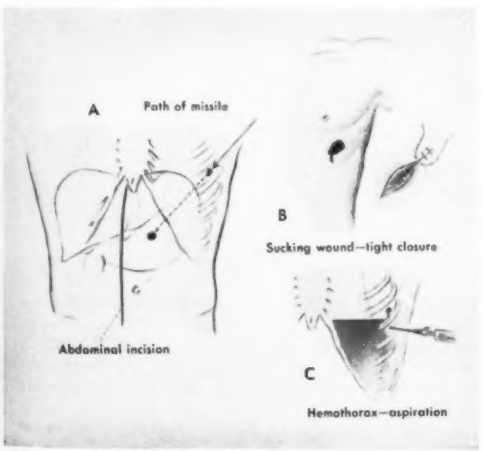


FIGURE 8. **Anastomosis of femoral artery.** The femoral artery was divided, requiring end-to-end anastomosis. After completion of the anastomosis, the wound is débrided. A layer of muscle is sutured over the vessel and the remainder of the wound is allowed to remain open.

THORACIC and THORACICO-ABDOMINAL WOUNDS

Thoracic and thoracico-abdominal wounds are particularly important because of the altered cardiorespiratory physiology that occurs after such injury. Sucking wounds of the chest are sealed off with a layer of petrolatum gauze and covered with an occlusive dressing as soon as a patient is seen. Thoracentesis may be required to relieve respiratory distress or a pneumothorax or a hemothorax. In multiple fractures of the ribs, a tracheotomy decreases the complications of atelectasis and assists in maintaining a clean tracheobronchial tree. Intercostal nerve block decreases pain and allows better respiratory exchange. Most wounds of the chest can be managed by multiple needle aspirations. Thoracotomy is not performed unless there is uncontrolled hemorrhage, esophageal perforation or cardiac tamponade. Foreign bodies can be removed later.

A conservative approach to thoracico-abdominal wounds is also indicated. Usually the injury of the chest can be treated by multiple thoracenteses and the abdomen can be explored through an abdominal incision. All wounds of the diaphragm are closed to prevent empyema. Combined thoracico-abdominal incisions carry a high fatality rate and unless specifically indicated are not used.



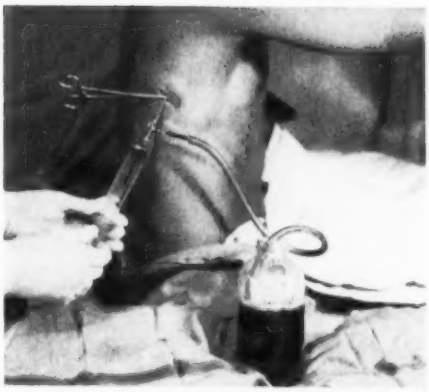


FIGURE 10. Pneumothorax and hemothorax are best treated by needle aspiration. Procedure has priority to correct deranged cardiorespiratory physiology before further procedures are considered.

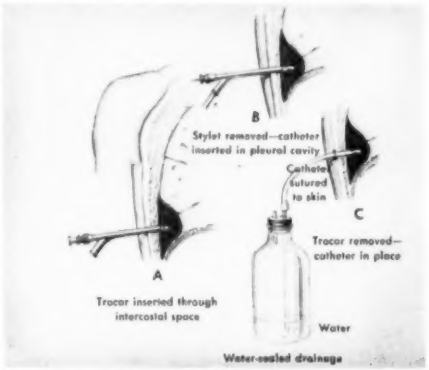


FIGURE 11. **Tube thoracotomy.** Multiple thoracenteses for hemothorax are preferred to tube thoracotomy. In some instances, when needle aspiration cannot be done frequently enough to keep the pleural cavity dry, a large catheter is inserted through a trocar and attached to water-seal drainage. Tube is removed before evacuation. Infections in pleural cavity follow tube thoracotomy more often than multiple thoracenteses.

FIGURE 9. **Thoracico-abdominal injuries.** The path of the missile is usually through the diaphragm and into the abdomen. Hemothorax is treated by needle aspiration. Sucking wounds of the chest are closed tightly, and thoracotomy is not indicated unless undue hemorrhage occurs in the chest. The abdomen is explored through a longitudinal incision.

LIVER and ABDOMINAL WOUNDS

The chief problems following liver injury are control of hemorrhage and prevention of bile peritonitis. Massive injuries to the liver are difficult to handle and result in a high mortality. Large through-and-through sutures may suffice to control hemorrhage, but in some very severe injuries a large pack may have to be inserted although it is undesirable. If the gallbladder is injured appreciably, it is removed. If there is a laceration of the common duct, it is closed transversely over a catheter or T tube.

Whenever an injury to the contents of the peritoneal cavity is suspected, an exploration is performed. Perforating wounds of the abdomen require a long incision to permit thorough, rapid examination. In cases of severe hemorrhage, the small intestine is eviscerated to facilitate rapid exploration and control of bleeding. All organs must be examined. After closure of the abdominal incision, the wounds in the abdominal wall are débrided and allowed to remain open.

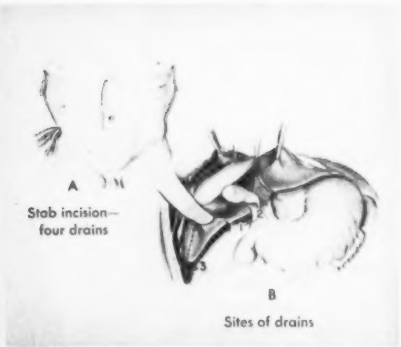


FIGURE 12. **Drainage of liver wounds.** Bile peritonitis may develop unless wounds of the liver are drained. Drains are brought out through a stab incision and remain in place at least 14 days. Four drains are inserted: (1) in the foramen of Winslow, (2) in the subhepatic space, (3) behind the posterior surface of the liver, and (4) above the dome of the diaphragm.

FIGURE 13. **Laceration of the liver.** Simple laceration of the liver without bleeding requires only drainage of the area. All extensive lacerations are repaired by deep figure-of-eight sutures of chromic catgut. In some instances it may be necessary to pack the wound with GELFOAM® gauze to assist in hemostasis.

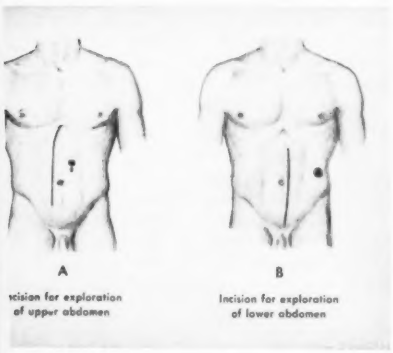


FIGURE 14. **Abdominal incisions.** Incisions in the abdomen should be sufficiently long to permit a thorough examination. In the upper abdomen, they start at the costal margin and go well below the umbilicus. In the lower abdomen, they start above the umbilicus and extend to the pubis. Incisions are not made through the missile wound.

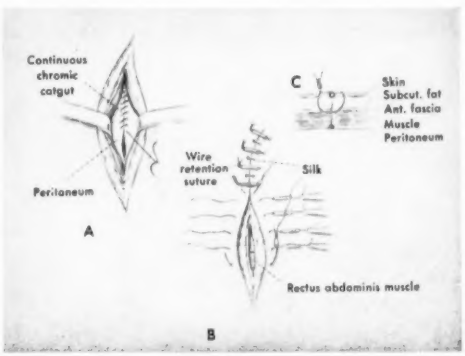


FIGURE 15. **Closure of the abdominal incision.** The diagram shows a method for closing the abdominal incision after acute injury that proved most acceptable in Korea. Continuous chromic catgut is used for the peritoneum, and wire retention sutures are used for the skin, subcutaneous tissue and fascia. In some instances a few silk sutures are used to pull the skin margins together.

COLON and RECTAL WOUNDS

CASE 5. A 22 year old soldier sustained injuries to the lower colon and rectum from mortar-shell fragments. The fragments penetrated his back. He was admitted to the forward hospital three and one-half hours after injury. Gross blood was oozing from the rectum. Operation revealed penetrating wounds low in the rectum and at the rectosigmoid junction, and four perforations of the ileum. A single layer of interrupted, nonabsorbable sutures closed the perforations. The wound in the rectosigmoid was closed, but the wound low in the rectum was not explored. A two-stoma defunctioning colostomy was carried out and the presacral area was drained.

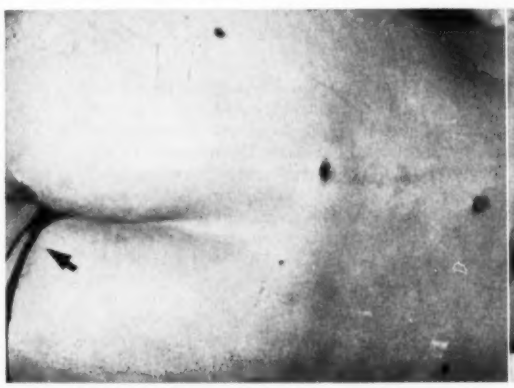


FIGURE 16a. **Multiple penetrating wounds of the sacral region.** Blood oozing from the anus is evidence of injury to the rectum.

FIGURE 16b. **Drainage of the presacral space.** After injuries to the rectum, the presacral space is drained. Otherwise, cellulitis may develop in the presacral space and extend anteriorly, causing severe pelvic infection.

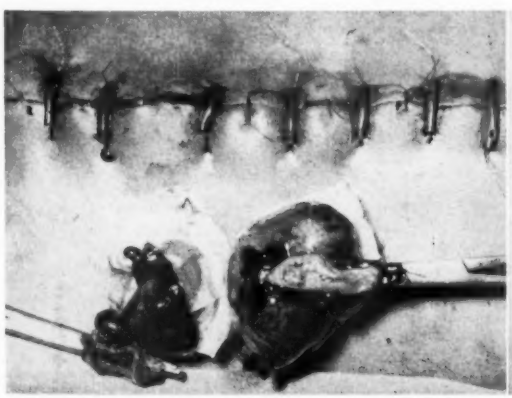


FIGURE 16c. **Defunctioning colostomy.** In all wounds of the rectum, a defunctioning colostomy is performed. A two-stoma colostomy is preferable to avoid spillage of fecal contents into the distal segment.

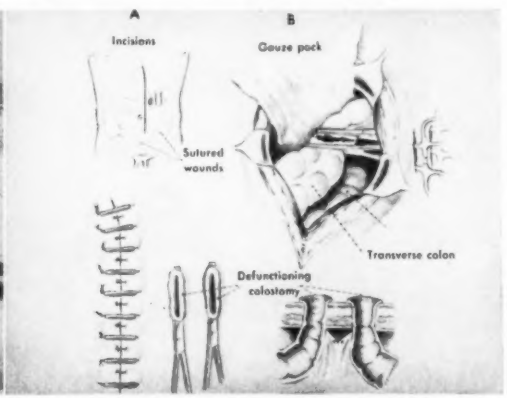


FIGURE 17. **Multiple wounds of the colon.** The distal wounds are closed and the proximal wound area is brought out as a defunctioning colostomy. Healing will occur in the distal sutured wounds because the bowel is put at complete rest.

PERFORATED VISCUS...

As soon as the abdomen is opened and the hemorrhage is controlled, exploration may be started. Perforations of the intestinal tract may be marked by applying Babcock clamps. This closes the opening temporarily and prevents further contamination. The entire intestinal tract is explored before any repair is started. Simple perforations are closed, but multiple lacerations may require resection. Drainage of the abdomen is not indicated unless there is retroperitoneal injury or injury to the biliary system.

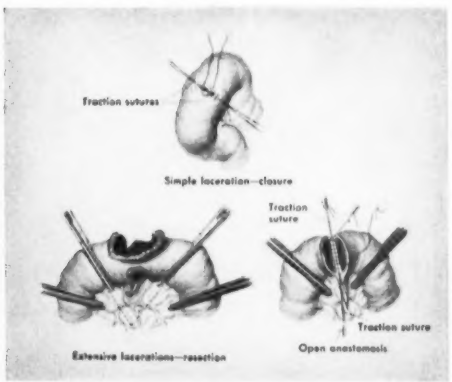


FIGURE 18. **Wounds of the small intestine.** A single layer of sutures placed transversely closes simple lacerations of the small intestine. Débridement of the wound edges only causes increased hemorrhage. Extensive lacerations require resection. The most expeditious closure after resection is an open anastomosis.

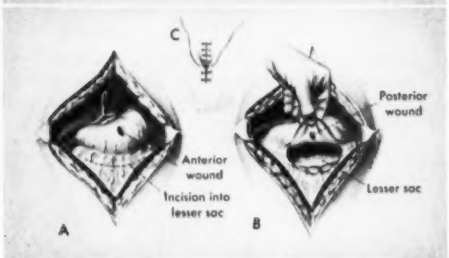


FIGURE 19. **Wounds of the stomach.** In all wounds of the stomach, an incision must be made through the gastrocolic ligament to permit complete examination of the posterior surface. The stomach wall is closed by two layers of interrupted, nonabsorbable sutures.

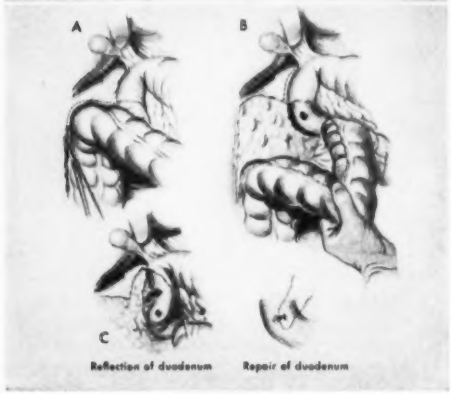


FIGURE 20. **Wounds of the duodenum.** Whenever injury to the duodenum is suspected, the hepatic flexure of the colon must be freed and the duodenum must be examined thoroughly. If there is any evidence of damage, the duodenum is immobilized in order to inspect its posterior wall thoroughly. Wounds of the duodenum are closed transversely with two layers of interrupted sutures, and the area is then drained.

NECK WOUNDS...

Wounds of the neck are carefully inspected to determine the path of the missile. Roentgenograms are required to locate any retained fragments. The chief problems of wounds of this region are injuries to the carotid vessels, the trachea or esophagus. Immediate repair of carotid injuries is followed by a high fatality rate. If hemorrhage has ceased, operation on the carotid vessel should be deferred until several months later. When there is excessive swelling of the neck and respiration is impaired, a tracheotomy must be performed.

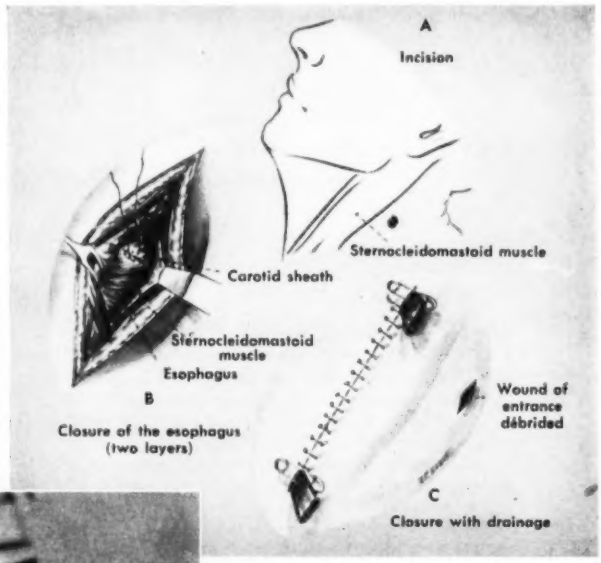


FIGURE 21. **Wounds of the neck.** When esophageal involvement is suspected, exploration must be performed. Perforation of the esophagus is closed by two layers of interrupted, nonabsorbable sutures. The incision is closed after adequate drains are inserted.

FIGURE 22. **Tracheotomy.** Tracheotomy not only assures an airway, but it offers a means of maintaining tracheobronchial toilet. This excellent safety measure should be carried out on the slightest indication.

UROGENITAL INJURIES

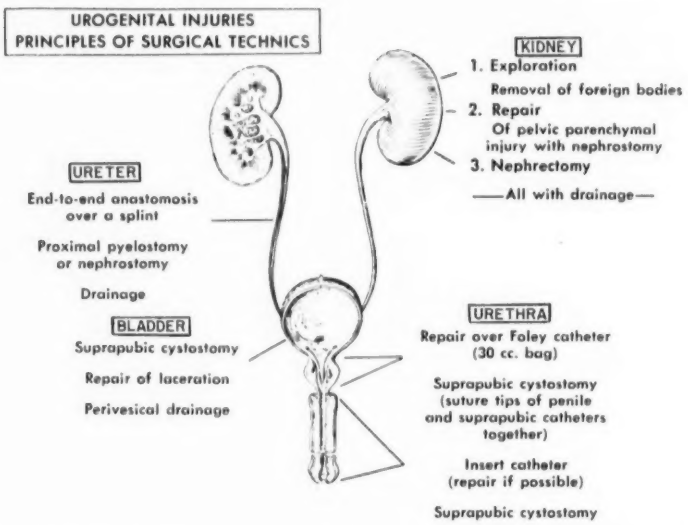


FIGURE 23. **Urogenital injuries.** A conservative attitude is maintained in injuries to the kidney. After exploration, every attempt is made to repair injuries rather than to perform nephrectomy. When parenchymal injuries are repaired, a nephrostomy is performed. After completion of all operative procedures about the kidney, the area is drained.

Lacerations of the ureters are repaired by end-to-end anastomosis over a splint, followed by a proximal pyelostomy or nephrostomy.

Lacerations of the bladder require suture of the laceration with suprapubic cystostomy and perivesical drainage.

If injury occurs in the proximal portion of the urethra, a Foley catheter is inserted and a suprapubic cystostomy is performed. The tips of the penile and suprapubic catheters are sutured together to protect against displacement. In major injuries of the distal urethra, a similar procedure is performed and the laceration of the urethra is repaired whenever possible.

SUMMARY

The initial management of the severely wounded requires early resuscitation, careful preoperative preparation, expeditious surgery and diligent postoperative care. During a catastrophe, frequently the exigencies of the situation do not permit adequate postoperative care. The surgical technics employed must therefore be of such nature that untoward complications will not result if only minimal observation is possible after operation.

Diagnosis of Diabetes

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It is now generally considered most desirable to diagnose and treat diabetes mellitus as early as possible. To accomplish this, it is important to recognize the slow and insidious course of the disease in its early stages. Diabetes frequently runs half its course solely as a biochemical disturbance without clinical manifestations and may do so for over one or more decades before discovery. This may help explain why fully 20 per cent of diabetics have diabetic complications at the time the clinical diagnosis is made.

To discover the disease earlier, an understanding of the biochemical alteration of its early stages is necessary. For comparison, figure 1 depicts the blood sugar curve, after breakfast, of a normal individual with a normal renal threshold. The measure of stress on the carbohydrate disposal mechanism is the blood sugar maximum, which usually occurs one hour after a meal (or even later in untreated diabetics). The urine maximum occurs two hours after the meal and any glycosuria is shown by the shaded area in the box below the base line.

In its earliest stage, diabetes has only biochemical manifestations. Figure 2 illustrates one of the earliest detectable stages of diabetes, that of postprandial hyperglycemia. Clinically it is characterized by a rise in the blood sugar one hour after a meal to abnormal levels. The normal one hour after meal values rise with age, being approximately 100 mg. per cent plus the age. However, a blood sugar of 150 mg. per cent or over is abnormal at any age, although it is still below the normal renal threshold. An even milder degree of carbohydrate intolerance can be detected by a glucose tolerance test, even at the normal postprandial blood sugar stage. Determining the fasting blood sugar or examining the urine is

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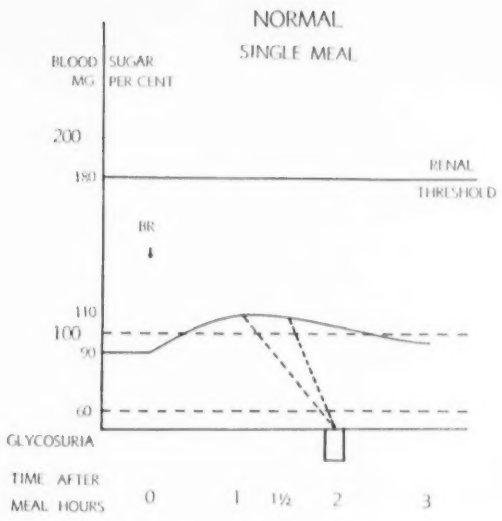

FIGURE 1. Normal blood sugar curve after a meal with adequate carbohydrate content, showing normal renal threshold and absence of glycosuria (box below base line).

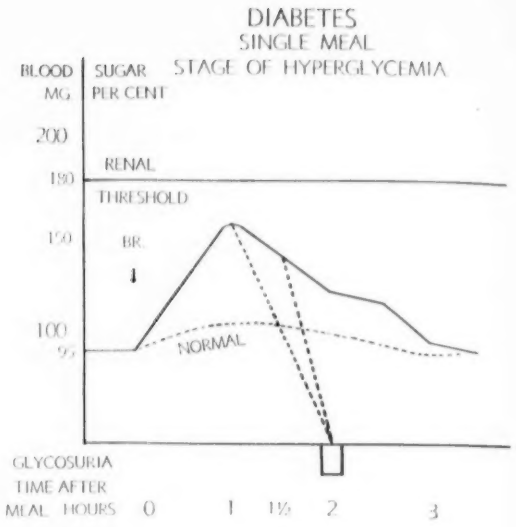

FIGURE 2. Blood sugar curve of diabetic at hyperglycemic stage, showing renal threshold not exceeded and postprandial (one hour) blood sugar suggestive, but not diagnostic.

useless diagnostically in either case.

Figure 3 illustrates a later stage, that of intermittent postprandial glycosuria. The blood sugar has risen postprandially above the renal threshold and glycosuria has appeared, but only after meals. Unless collected at the proper time, one chance urine specimen could be positive and 50 others negative. The fasting blood sugar is always normal at this stage, too. This emphasizes the need to follow up any single instance of glycosuria by a glucose tolerance test, regardless of how many negative urine tests have preceded or succeeded it. Also, it shows the uselessness of the usual hospital fasting urine tests for diabetes screening purposes. At this stage the urine test can be negative for sugar even two hours after eating if the carbohydrate content of the meal is inadequate. Finally, an intercurrent disease may cause a patient's diabetes to worsen temporarily; for example, progressing from the first hyperglycemic to the second glycosuric stage. After recovery, the condition may then revert. Repetition of urine tests after a positive test has been noted does not further diagnosis; only blood tests give a definite answer.

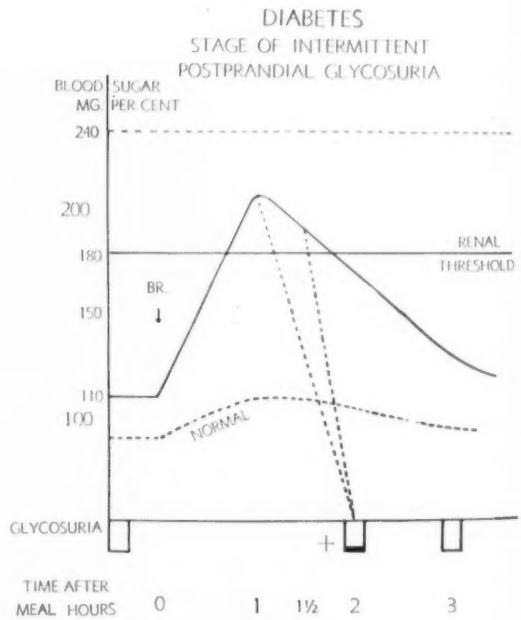

FIGURE 3. Blood sugar curve of diabetic at intermittent postprandial glycosuric stage, showing renal threshold exceeded only at the peak (one hour) after meal with consequent single postprandial glycosuria. An elevated renal threshold would not be exceeded. Blood sugar test one hour after meal is diagnostic.

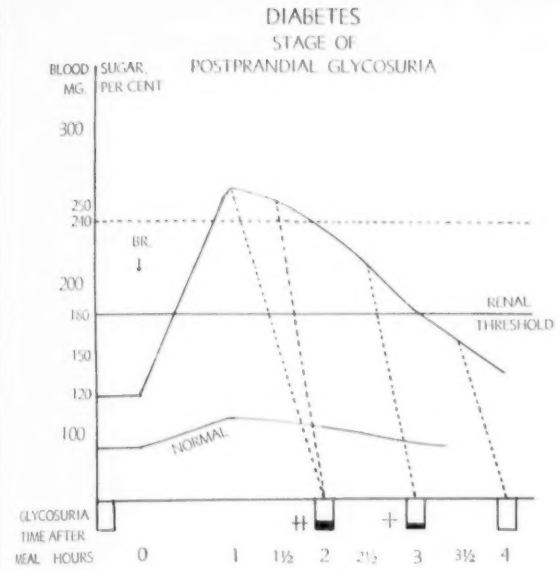

FIGURE 4. Blood sugar curve of diabetic at postprandial glycosuric stage, showing both normal and elevated renal thresholds exceeded for a longer period of time. Several postprandial urines contain sugar. Fasting blood sugar still may be normal and symptoms absent. Blood sugar test one to two hours after meal is diagnostic.

Figure 4 illustrates one stage further, that of postprandial glycosuria. In this stage, there is a still greater chance of detecting glycosuria by chance urinalysis, yet the fasting blood sugar may still be normal even at this relatively advanced stage. In this figure the dotted line depicts an alternative, elevated renal threshold as a reminder that even in the silent asymptomatic stages of diabetes the renal threshold may rise as a complication of the disease. In such instances, detection is postponed because glycosuria is depended on to detect diabetes. It is worth emphasizing that glycosuria is the first manifestation of diabetes in over 50 per cent of patients.[1] Symptoms are present in only a small minority of patients at this stage.

Figure 5 shows the stage of constant glycosuria, the first stage in which symptoms are certain to be present in practically all cases. Over-all, only one-third of diabetics are detected by symptoms. At this stage a glucose tolerance test is unnecessary for diagnosis; all Benedict's urine tests are yellow or orange and a blood sugar determination at any time of day is diagnostic.

The progress of untreated diabetes in the adult spans decades. Information is scarce about the hidden hyperglycemic stage, while the later stages are terminated earlier because of symptoms. It takes an average of 3 to 10 years for the disease to progress from a green test postprandially to an orange test, with or without symptoms.[1]

It is important to diagnose diabetes at the asymptomatic stages. Which tests are most useful to this end? The fasting blood sugar is almost invariably normal and therefore useless diagnostically. The one hour after meal blood sugar is less sensitive by fully 50 mg. per cent than the glucose tolerance test at the one hour maximum. Also, due to its dependence on digestion, it is too variable. The glucose tolerance test is the method of choice. It requires that the patient be on a high carbohydrate diet for at least three days before the test. However, because of the inconven-

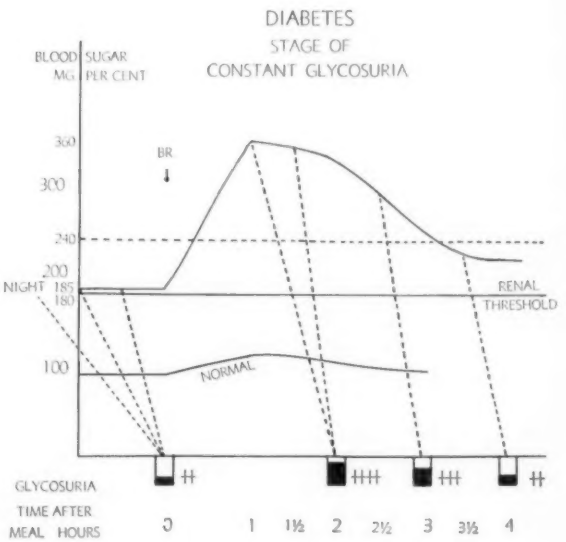

FIGURE 5. Blood sugar curve of diabetic at constant glycosuric stage showing entire blood sugar curve exceeding the normal renal threshold. All urines, including fasting, now contain sugar. Blood sugar test at any time is diagnostic, and symptoms are usually present.

ience of the full test, some less diagnostic single blood sugar test is frequently substituted. To obviate this disadvantage, we have used a simple modification at the Beth Israel Hospital in Boston for the past eight years. We prescribe the usual 100 gm. of dextrose as a 20 per cent solution to be taken orally, and perform blood sugar and urine tests at one and at two and one-half hours after the dextrose is administered.* Thus, if the patient drinks the solution at home and has two blood sugar tests, spending a total of one and one-half hours in the physician's office, the diagnostic return is equal to that of the full test. In addition, the urine tests afford a clinical estimate of the renal threshold on which to judge the validity of using urine tests subsequently as convenient home indexes of therapeutic progress. Finally, there has recently been proposed the diagnostic use of the single two hour blood sugar test after 100 gm. of glucose. This may have validity not only for screening purposes but also for office diagnosis.[2,3]

There are several practical concepts in diagnosing diabetes which require special emphasis. First, the diagnosis should be interpreted to the patient in an unequivocal manner. It should be expressed in terms of diabetes or no diabetes, and not in such a vague and loose phrase as "a little sugar in the blood or urine." Patients are only too anxious to misinterpret a physician's tendency to minimize the significance of the findings. Secondly, the patient too frequently interprets regulation to the point of aglycosuria as "cure" of the disease. In this, the patient too often finds support from the physician if normoglycemia is achieved. This misconception is further compounded if a glucose tolerance turns out to be normal. It is not generally realized that this occurs in a well-treated mild or moderate diabetic. It is wiser to emphasize to the patient that once diabetes has been proved, it can be regulated but not cured. And it is a wiser policy for the physician to accept a diagnosis made elsewhere, if reasonably certain, than either to doubt it or reopen the question.

*Normal values: one hour, not over 180 mg. per cent; two and one-half hours, not over 125 mg. per cent (Folin-Wu).

Once the diagnosis has been made, there is usually no need ever to repeat the glucose tolerance test. The one hour after meal blood sugar, not the glucose tolerance test, serves as the index of regulation in a treated diabetic. In such a patient it may require not three days, but weeks or months of a normal or high carbohydrate diet for a glucose tolerance to become abnormal again. It is certainly undesirable to break down the improved carbohydrate tolerance of such a treated patient unless absolutely necessary. Unfortunately, we are sometimes forced to do this because of clinical errors. The most frequent mistake is to place a patient on a reducing or diabetic diet after finding glycosuria alone without proper diagnosis by blood tests.

Interpreting the results of the glucose tolerance test may not be simple. First, let us consider the fully abnormal test, i.e., both at the peak and two and one-half to three hour points. If it is mildly positive and accompanied by thyrotoxicosis or hepatic disease, final diagnosis may have to be based on a test made after the complications have been eliminated. In practice, confirmatory tests such as the intravenous technic alone or combined with serum phosphorus determinations have not proved successful.[4]

Older patients show a high incidence of abnormal glucose tolerance tests. It is still uncertain whether the deficiency is pancreatic in origin or due to senile failure or to the inadequacy of one or more of the many enzymes and hormones involved in normal carbohydrate metabolism. Intercurrent complications (infections, operations, myocardial infarction, etc.) which may be accompanied by abnormal tolerance curves also present a problem in interpretation. While many patients may revert to normal in days or weeks, long-term follow-up of such cases shows a high incidence of subsequent diabetes. It is wiser to consider and treat them as mild diabetics. The same holds for pregnant women. It is now customary to use the same criteria of normalcy for testing pregnant patients as for the non-pregnant, and the test is known to revert to normal within hours to days after delivery.[5]

The most challenging problem is the curve

with only one of the two areas (peak or duration), but not both, abnormal. This occurs in as many as 15 per cent of all glucose tolerance tests. Rabinowitch[6] has shown that when a large group of such patients was followed for 10 years, 30 per cent of them became clinically diabetic, while the subgroup of those with obesity or a family history of diabetes showed almost a 50 per cent incidence.

Therapeutically, we would have to be consistent and consider these as mild or probable diabetics, too. We can do this relatively simply since a large percentage of them are obese. Decrease of diet caloric content for weight reduction as well as of starch content for the diabetes will usually correct the biochemical abnormality. Starch content is reduced from 65 per cent, the proportion present in the average American diet, to 45 per cent in the average diabetic diet.

It would be important to develop clinical technics to clarify such atypical glucose tolerance tests. Actually, some curves may be atypical because Folin-Wu rather than true glucose blood sugar methods are used. In others, it may be due to the fact that the peak of blood sugar in some patients may occur at a time other than at exactly one hour after eating. In others, it may be due to nausea or aberrations in gastrointestinal motility. An intravenous technic would obviate this condition. Moreover, it has recently been shown that the resultant curve after an intravenous injection can be analyzed mathematically to yield an individual index of glucose disposal by the body.[7] This type of curve has been shown to separate the mild diabetics from normal persons more decisively than the ordinary oral glucose tolerance curves. In performing an intravenous glucose tolerance test, it is best to avoid technics involving fast injection of glucose and production of immediate high blood sugar levels. The latter are capable of activating a specific type of insulin antagonist which

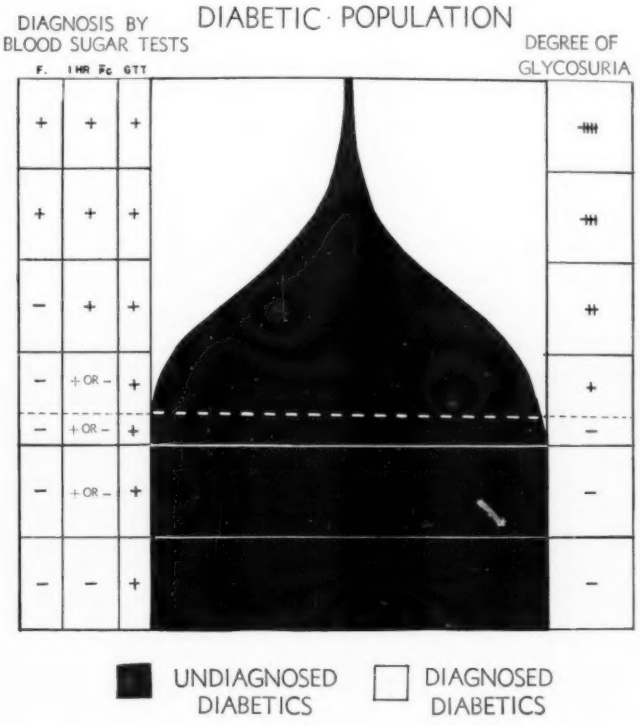

FIGURE 6. Schematic representation of entire diabetic population. (Shaded area represents undiagnosed, unshaded diagnosed.) The order of severity increases from bottom to top, with increasing degrees of glycosuria and ease of diagnosis. The effect of an alternative, elevated renal threshold (dotted line) on diagnosis is also shown.

changes the effective activity of the body's insulin and the resultant rate of the glucose disposal.[8]

Patients with conditions causing nausea or decreased intestinal absorption will yield false negative results. Such conditions include vomiting of pregnancy, myxedema and Addison's disease. Negative results due to these conditions can be avoided by using an intravenous technic.

Figure 6 shows in schematic form the total diabetic population, both the discovered (unshaded) and undiscovered (shaded). The stages increase in severity from bottom to top. The ease of diagnosis and the proportion diagnosed increase in the same direction. The dotted line represents those with elevated renal threshold and shows its adverse effect on detection in this group. The obvious challenge lies in the one million undiagnosed diabetics, especially those below the renal threshold line. To detect these cases would require widespread use of glucose tolerance tests or postprandial blood sugars. Practicing physicians cannot as yet perform these tests on all their patients. However, they could discharge their obligation to their patients more fully by proper selection of candidates for these tests among patients without glycosuria. Selection should be based on these criteria: obesity, family history of diabetes, presence of previous glycosuria, obstetric history of prenatal fetal mortality or large babies (over 10 lb.), or such symptoms or complications suggestive of diabetes as pruritus vulvae, furunculosis or premature arteriosclerosis or cataracts. A combination of more than one of these conditions would be as suggestive as glycosuria.

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Postgraduate Clinical NOTES

40. HIGH BLOOD PRESSURE

Thirteen per cent of the deaths from cardiovascular disease in the United States are definitely due to high blood pressure. Many more deaths which cannot be strictly classified are attributable to hypertensive causes. An additional 30 per cent of heart disease deaths cannot be accurately classified as due to arteriosclerosis or hypertension, respectively, but they are due to one of the two, or both.

Of the estimated 10 million persons with some form of cardiovascular disease, fully 4,600,000 have high blood pressure. Of the young men examined by Selective Service during the years 1940-44, 165,000 were rejected because of high blood pressure.

Hypertension is far more common in women than in men, by a ratio of about 2 to 1. On the other hand, hypertension is less frequently fatal for women.

Public Health Reports, January 1955, p. 63

A Rational Approach to Normoglycemia in Treatment of Diabetes Mellitus

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UNTIL recently the treatment of diabetes mellitus was concerned chiefly with relieving symptoms and preventing acidosis. However, the improved control made possible by the advent of modified insulins during the past 15 years has resulted in increasing evidence which suggests that meticulous and continuous normoglycemia now enables us to reduce the incidence and severity of diabetic complications.[1-6] Despite insistence on the harmlessness of hyperglycemia by a small but vocal minority, 93 per cent of the membership of the American Diabetes Association have indicated that their goal in the treatment of diabetes mellitus is a normal blood sugar or a sugar-free urine.[7] The treatment of the disease now has the immediate aim of producing and maintaining normoglycemia.

While normoglycemia cannot be achieved in all diabetic patients, many of whom are notoriously "difficult," optimal results can be obtained by a rational approach to four basic aspects of treatment: (1) education of the patient, (2) diet, (3) insulin, and (4) development of an adequate patient-physician relationship through which the other treatments are made more effective.

Education of the Patient

While normoglycemia is theoretically possible for 90 per cent of all diabetics, not more than 20 per cent actually attain such a degree of regulation.[3,8] The discrepancy between what is possible and what is achieved is sometimes due to factors out of the physician's control. Much more frequently, however, the patient's failure to achieve regulation results from the physician's preoccupation with purely physiologic aspects of regulation to the ex-

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clusion of maximal efforts toward the better management of the patient with whom, after all, rests the day-to-day responsibility for carrying out the prescribed regimen.

Education of the patient, which is the initial therapy, must be a highly organized, carefully planned program in which the physician fully utilizes the dietitian, chiropodist, visiting nurse, and all other ancillary resources. Patients may be taught in small groups as well as individually, not only by the doctor at each visit but also through class lectures, pamphlets, filmstrips and demonstrations. Since the patient tends to forget anything which reminds him of his illness, teaching must be a persistent and continuing process for the duration of the disease.

That such considerations are not merely academic is shown by the fact that among the 1500 patients of the Abraham Rudy Diabetic Clinic at the Beth Israel Hospital in Boston, such a program has clearly contributed to better control and strikingly decreased the incidence of low thigh amputations. Diabetic acidosis is so rare among these clinic patients that most instances of coma in the hospital come from the community at large. In an eight year period, of the six low thigh amputations performed on elderly diabetic clinic patients, only one might have been prevented, while in the general hospital practice fully 50 per cent of the amputations might have been avoided by a better-instructed patient.

The education offered to patients in the diabetic clinic of a teaching hospital is available in the general community through visiting nurses' associations, public health demonstrations and programs sponsored by United Community Services. Similar facilities have been and will continue to be set up in smaller communities, utilizing the local hospital as the teaching center to which patients may be referred by their private physician.

The Diabetic Diet

If we assume that the patient's endogenous insulin and metabolic thermostat are relatively constant, if activity varies little, and if the dosage of exogenous insulin is unchanged, then variations in the blood sugar from day to day usually result from wide variations in diet, particularly in carbohydrate intake. Such variations are notorious among diabetic patients, partly because many were compulsive overeaters even before the onset of diabetes, in some measure because one reaction to an involuntary curtailment of dietary freedom is rebellion, and in part because diets are often too complicated, alien, rigid and exacting.

Indeed, patient discomfort with rigid diets has influenced a minority of physicians to go to the opposite extreme in permitting or advocating the so-called "free" diet. Neither extreme is warranted. The variation of the carbohydrate content of foods is such that a plus or minus 10 per cent variation in diet from day to day constitutes reasonable constancy. Adherence to a diet within these limitations is perfectly consistent with normoglycemic control. These simple facts, which are based on clinical experience, point up the semantic difficulty which has led some physicians to confuse "liberal" with "free" and "constant" with "irksome," in respect to diets. Modern insulin makes it practical for the diabetic diet to be both liberal and reasonably constant. All the basic foods can be included, but the more limited diets should be supplemented by daily polyvitamin capsules. Whenever possible, of course, obese patients should be helped to reduce and too-thin patients helped to gain weight. However, the physician must be able to accept failure in occasional patients and not endanger other therapeutic efforts by stubborn insistence on a weight change which the patient obviously cannot achieve. In practice, in 90 per cent of the diets prescribed, the carbohydrate content will vary from 150 to 250 gm. per day, the protein from 70 to 100 gm., and the fat from 70 to 120 gm. depending on age, sex, size, health, work and other factors involved.

Simplification of diet therapy will also add to patient cooperation. Since the sugar content of carbohydrate foods normally varies by a factor of plus or minus 10 per cent, the weighing of diet foods on gram scales may be supplanted effectively and profitably by simple household measures. The educational advantage which accrues from the use of scales

is greatly increased by substituting sufficient personal instruction. Another simplification is the grouping of foods into relatively few exchange categories by disregarding minor variations in carbohydrate, protein and fat content. Such a simplified unit exchange system has been published.[9]

Acceptability is an additional aspect of diet which often receives too little attention. The prescription of a completely alien way of eating is an invitation to the patient to abandon his diet. To make a diet acceptable involves an understanding of the patient's likes and dislikes, his food habits, and his preferred pattern of eating. One must also consider whether the patient is a laborer or sedentary clerk, whether he can afford to buy the prescribed foods, whether he works nights, lives with his family or alone in a furnished room, or eats all his meals in restaurants.

An effective approach to making the diet acceptable is to obtain a sample 24 hour food history at the very outset. This will usually provide all the needed information. The diet prescription can then be adapted to the needs of the individual whom it will serve much better than stock printed diet forms.

A diet which is liberal yet reasonably constant from day to day, which is based on household measurements and simplified exchanges, and is tailored to the individual's requirements constitutes an important contribution to cooperation and the maintenance of good control.

Use of Insulin

Half of all diabetic patients require insulin as well as diet. In general, it is better to use insulin from the start in borderline cases and to be able to omit it later, than to avoid its use and eventually make the patient feel he is worse by insisting on it when diet therapy alone has failed.

Perhaps 90 per cent of patients needing insulin can be equally well controlled by any of the modern preparations, whether globin, NPH, lente, or protamine zinc insulin either alone or in combination with regular insulin. A few diabetics, usually younger individuals with large insulin requirements, show frequent abrupt fluctuations in carbohydrate metabolism and have unpredictable blood sugar content which is difficult or impossible to keep within normoglycemic limits. These patients are labeled "brittle" diabetics, and one must often be satisfied merely to avoid acidosis and severe hypoglycemia in their cases. An occasional "brittle" diabetic will be found quite stable if a protamine zinc-regular insulin mixture is used instead of the NPH or globin insulin. In most "brittle" diabetic patients, however, no single dosage of insulin gives consistently satisfactory results. At present such patients are best treated by a flexible insulin schedule based on NPH or protamine zinc insulin in the morning, with varying supplements of regular insulin during the day or evening according to the urine test.

The most recently developed preparation, lente insulin,[10] has a curve of action very much like that of NPH insulin, but in some patients lente insulin appears to have a slightly longer duration and smoother action. Nevertheless, although various clinics have been highly successful with each of the available insulin preparations, the insulin of choice at present is NPH. Whatever the intermediate insulin, the procedure of adjusting the dosage to the needs of the new diabetic patient is by a method of successive approximations.[11] An arbitrary small initial dose of NPH is prescribed and is then supplemented by regular insulin before lunch and dinner according to the urine test. Since the cumulative effect of a daily dose of any 24 to 36 hour insulin cannot be judged at less than three day intervals, changes in insulin dosage should not be made more frequently. On the fourth morning, therefore, the dose of NPH is increased by the same number of units as was needed in the form of regular insulin supplements on the previous day. This increased dose of NPH is again supplemented by regular insulin before lunch and dinner for another three days, and the cycle repeated until the urine test is negative before meals. At this point regular insulin is omitted, and the dose of NPH insulin is gradually increased until urine tests become blue two hours *after* breakfast. The end point in the hospital is a blood sugar reading

of less than 200 mg. one hour after breakfast. Increased physical activity following discharge from the hospital is depended on to bring this value to between 160 and 180 mg.

In all patients, before regulation is considered complete, two additional procedures are needed. A fasting blood sugar determination is obtained to make certain that the duration of insulin effect is adequate, and the one-hour-after-breakfast blood sugar is compared with the two-hour-after-breakfast urine test to obtain a rough idea of the renal threshold.

In a few patients, it will be found that, while the blood sugar and urine tests are satisfactory through most of the 24 hours, an excessive rise of the blood sugar occurs after breakfast. This is best corrected by replacing some of the NPH insulin by regular insulin, and mixing the two in the same syringe for more rapid action than is possible with the NPH insulin alone.

A few patients will show the reverse difficulty with good control through the early part of the day but a rising blood sugar during the night, with prebreakfast glycosuria. This indicates that the duration of action of NPH insulin in these patients is not sufficiently prolonged. Such patients are better handled by a mixture of two and one-half to three parts of regular insulin to one part of protamine zinc insulin taken before breakfast.

Elderly mild diabetics who require a small dose of insulin are usually well controlled by any of the intermediate or long-acting insulins.

When regulation has been completed, the patient is asked to insure the maintenance of good control by testing his urine two hours after breakfast several times a week. This will usually disclose the maximal spill of the 24 hour period, because the lowest ebb of carbohydrate tolerance is reached at the end of the overnight fast. Patients who work may test the urine two hours after the evening meal. In either case, occasional tests two hours after other meals will provide a further check as to whether the patient's urine is sugar-free at other times of the day as well.

It should be emphasized that the fasting blood sugar and fasting urine studies are as misleading with respect to regulation as they are with respect to the diagnosis of diabetes. A negative fasting urine test merely indicates a blood sugar at some level below the renal threshold, which in older patients may be 200 to 250 mg. A normal fasting blood sugar will indicate that the duration of insulin effect is adequate, but it will not disclose whether the dosage or type of insulin is adequate to control the diabetes after a meal.

Management of the Patient

If 90 per cent of diabetics could attain normoglycemic control, why should actual performance so often fall short of the theoretical results? No single answer applies to all instances in which this question can be raised, but the usual and simple explanation is that most poorly controlled patients do not follow their diets. The causes of this unrealistic behavior are complicated and deeply rooted in the character of the individual. They involve, among other factors, the patient's reaction to a chronic illness, identification with diabetic relatives who have suffered complications, deprivation of the tension-relieving pleasure of free eating, and the need to relate to the doctor, as an authority figure—all modified or determined by the patient's basic personality and life situation.[12-14]

The chronic anxiety associated with these stresses finds expression in ways which are characteristic for each patient: in hostility, by projection of the responsibility for poor results, in provocative behavior, by denial of illness, by flight from medical supervision, etc.[12] Such "uncooperative" patients are often unrealistic not only with respect to the diet, but also with respect to urine testing, taking insulin, observing proper diabetic precautions during other illnesses and seeking adequate supervision.

In dealing with such patients, the physician also must take care not to be unrealistic. His feeling of frustration and failure, as well as other emotional currents which operate in both directions, may lead him to be punitive, threatening, unsympathetic or overcritical.

Those patients who are capable of improving their diabetic control will do so best with the help of positive, sympathetic, individual-

ized and patient treatment by the physician. Those diabetics who do not respond to such an approach will not respond to any approach, and if the physician does not drive these patients away by his own behavior, he will at least remain available to them for complications and in emergencies. Persuasion by threat of complications, to which physicians sometimes resort, rarely has long-term effectiveness and usually makes the patient unhappier than his disease.

Children and adolescents need particularly careful management. Their emotional problems are usually more intense, and their abilities to handle problems successfully are less well developed than in the adult. Psychiatric assistance in the management of youngsters should be sought promptly when the situation warrants it. Juvenile diabetics do not "grow out" of their problems; the problems simply go underground and emerge later as neurotic behavior.

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BOOKS RECEIVED

New books received are acknowledged each month. As space permits, books of principal interest to our readers will be reviewed more extensively. Reviews will be found in this issue starting on page A-112 and additional listings on pages A-46, A-60 and 421.

Obstetrical Roentgenology. By Robert Berman, M.D., Assistant Clinical Professor of Obstetrics and Gynecology. Edited by Claude E. Heaton, M.D., Associate Professor of Obstetrics and Gynecology, New York University College of Medicine, New York. 599 pages with 486 illustrations. 1955, F. A. Davis Company, Philadelphia. $12.50.

Counseling in Medical Genetics. By Sheldon C. Reed, Director, Dight Institute for Human Genetics, The University of Minnesota, Minneapolis. 268 pages. 1955, W. B. Saunders Company, Philadelphia and London. $4.00.

Leitfaden der Urologie; Für Studium und Praxis. By C.-E. Alken, M.D., Director of Department of Urology, University of Homburg/Saar, Germany. 163 pages with 82 illustrations. 1955, Georg Thieme Verlag, Stuttgart, Germany. $3.95.

The Hemorrhagic Disorders. By Mario Stefanini, M.D., Associate Professor of Medicine, and William Dameshek, M.D., Professor of Medicine, Tufts University School of Medicine, Boston. 368 pages with 147 illustrations. 1955, Grune & Stratton, Inc., New York and London. $11.75.

Advances in Internal Medicine. Edited by William Dock, M.D., Long Island College of Medicine, and I. Snapper, M.D., Beth-El Hospital, Brooklyn. Vol. 7. 311 pages, illustrated. 1955, The Year Book Publishers, Inc., Chicago. $8.50.

Peptic Ulcer; Diagnosis and Treatment. By Clifford J. Barborka, M.D., Associate Professor of Medicine and Chief, Gastrointestinal Clinics, and E. Clinton Texter, Jr., M.D., Associate in Medicine and Assistant Chief, Gastrointestinal Clinics, Northwestern University Medical School, Chicago. 289 pages with 33 illustrations. 1955, Little, Brown and Company, Boston and Toronto. $7.00.

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The Traumatized Patient; Evaluation, Preparation and Anesthetic Management

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TRAUMATISM is universal—it occurs without warning at any time and at any place. It is certain that almost every practicing physician will be called on at some time to treat a traumatized patient. With this in mind, we wish to emphasize certain principles relative to care of the traumatized patient.

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Evaluation of the Patient

When serious trauma has been sustained, the physician should always anticipate effects other than those on the body structures directly involved. To treat merely the local injury, without treating the patient as a whole, is to invite disaster. When the patient is first seen in the emergency room, how can one evaluate his general condition to determine when anesthesia and emergency operation can be undertaken with a relative degree of safety? This evaluation must be based on a history and physical examination. The history obtained from the patient or others should be brief but pertinent, including such items as recent illnesses, operations and any currently sustained drug therapy. Specific inquiry should be made into the present injury, noting when, where and how it occurred. Detailed information should be obtained regarding any previous emergency treatment.

A thorough, but gentle, physical examination should be made quickly. Blood pressure, pulse and respiration should be measured, and the results recorded. The appearance of the skin and mucous membranes should be noted with reference to color, temperature and degree of moisture. Likewise, the patient's men-

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tal state should be appraised relative to the degree of consciousness, pain and fear or anxiety.

Of paramount importance in evaluating the patient's condition is the estimation of the degree of shock present. When shock is fully developed and its classic symptoms and signs prevail, the diagnosis is simple. However, the presence of impending shock is much more difficult to determine, since there are few reliable indexes and the signs are often obscure.

Arterial blood pressure changes and reduction in circulating blood volume show a close correlation. Systolic blood pressures under 100 mm. Hg are associated with a reduced blood volume of 70 per cent of normal or less. Progressive reduction in pulse pressure also occurs as the degree of shock increases. Single determinations of blood pressure, pulse pressure and pulse rate are of little prognostic value. It is very important, however, to observe and record the trends of these findings.

Preoperative Preparation—Respiratory Problems

Respiratory difficulties are often the most urgent problems encountered in the recently injured patient. Respiratory arrest without prompt and efficient treatment very quickly results in death. Regardless of the cause of apnea, efficient artificial respiration must be instituted immediately. Manual methods of artificial respiration or mouth-to-mouth breathing are temporary expedients and should be used only until resuscitative equipment providing 100 per cent oxygen is available. Such equipment should be available immediately in the emergency room, clinic or hospital. However, unless a patent airway is maintained so that the oxygen can reach the pulmonary alveoli, resuscitation efforts may be wasted.

In patients who breathe spontaneously, the airway also should receive major attention. Untreated respiratory obstruction, regardless of cause, may result in sufficient hypoxia to endanger life. The comatose or semicomatose patient with a relaxed jaw may have airway obstruction caused by the tongue falling back into the oropharynx. Blood from maxillofacial injuries can obstruct the airway. Likewise, deformity or edema resulting from trauma to the larynx can embarrass respiratory exchange.

Simple elevation of the angles of the mandible often will relieve obstruction of the airway by the tongue. Foreign matter, such as blood, mucus or regurgitated stomach contents, should be aspirated promptly and carefully. Respiratory obstruction which does not respond to these measures may require the use of such mechanical means as oral or nasal airways or intratracheal tubes. When obstruction of the larynx exists, tracheotomy should not be deferred, but should be carried out promptly to avoid the deleterious effects of hypoxia.

Obstruction of the lower respiratory tract resulting from blood, mucus or regurgitated gastric contents should be treated by immediate tracheobronchial aspiration. This may be accomplished by the use of either a suction catheter or an aspirating bronchoscope.

Severe chest trauma should be carefully evaluated and appropriate corrective measures instituted. Injuries of this nature, because of the interference with cardiorespiratory function, often cause early, severe hypoxia which may threaten immediate survival or the ability to withstand surgical treatment.

Circulatory Problems

The greatest threat to life in cases of trauma usually comes from hemorrhagic shock. For purposes of discussion, shock can be considered a bodily reaction to an acute disproportion between the circulating blood volume and the capacity of the vascular tree. The classic signs of shock, such as low blood pressure, rapid thready pulse and cold clammy skin, are the late signs of circulatory deficiency. It has been estimated that as much as 20 per cent of the normal blood volume may be lost before any clinical effects become apparent. Whenever blood has been lost as a result of trauma, either to the tissues or body cavities or externally, the only ideal treatment is replacement with compatible whole blood.

In dire circumstances, low titer type O Rh-negative blood, preferably with A B substance added, can be used immediately without typing and crossmatching. However, a blood sam-

ple should be obtained prior to the administration of the blood so that any additional units of blood needed can be checked for compatibility.

Only whole blood supplies the red cells so vital for oxygen and carbon dioxide transport. To avoid permanent injury or death, a prompt and effective means of increasing the circulating blood volume should be instituted at once. If shock is profound and superficial veins are collapsed or inaccessible because of adiposity, a "cut-down" should be carried out and a large-gauge cannula tied into the vein. Intravascular replacement therapy is lifesaving, and time should not be wasted with uncertain or time-consuming methods of venipuncture.

The rate of administration and volume of blood to be given are dictated by the clinical response of the patient. When large volumes of blood have been lost and grave circulatory depression is present, replacement must be carried out rapidly. This may be accomplished by the use of pressure to force the blood into the vascular tree. By this method, a unit of whole blood may be administered in a few minutes. When near exsanguination has occurred or when customary methods of transfusion prove inadequate, intra-arterial transfusion may save the patient's life. By rapidly raising and maintaining the pressure in the aorta, blood flow to the heart and vital cerebral centers is promptly obtained.

The increased intra-aortic pressure may be obtained by intra-arterial or intra-aortic transfusion. In the operative case, it is a relatively simple matter to increase the thoracic intra-aortic pressure and blood flow to the heart and vital centers by either manual compression or the application of a tourniquet to the aorta. We wish to emphasize the value of compression of the aorta in cases where the heart is failing and the blood pressure is extremely low or unobtainable. Utilization of this technic will probably increase the number of successful cardiac resuscitation cases. A satisfactory effective blood pressure is much more easily obtained while cardiac massage is being carried out.

Human plasma is the ideal fluid for correcting a deficient blood volume resulting from burn, blast or crush injuries. In the treatment of hemorrhagic shock, it is often a lifesaving expedient to be used only until compatible whole blood can be made available.

Substances known as plasma volume expanders or extenders are now commercially available. These substances approximate normal human plasma with regard to osmotic pressure and viscosity. While not equal to plasma, they are easily available in sterile solution and can be used in emergencies, while specific replacement therapy is being made available.

Solutions such as glucose or normal saline are primarily indicated in the therapy of dehydration or electrolyte imbalance and are of value in establishing and maintaining a route for intravascular replacement therapy. In the treatment of traumatic shock, they may be dangerous because they produce a transient increase in blood volume and blood pressure and, hence, a false sense of security.

In addition to specific intravascular replacement therapy, certain adjuvant measures are useful in facilitating circulatory compensation. The head-down, or Trendelenburg, position is preferred in cases of shock, except when complicated by craniocerebral, thoracic or maxillofacial injury. In such cases, special positioning may be necessary. The Trendelenburg position utilizes gravity to improve the venous return to the heart and vital cerebral centers. If the degree of Trendelenburg position is too great or used too long, respiratory distress or excessive venous congestion may result. Dilated cutaneous capillary beds and sweating tend to produce a deleterious effect on an already deficient circulation. Although there is disagreement as to the value of administering oxygen in the treatment of traumatic shock, it should be utilized as an adjuvant therapeutic measure, since its use is often accompanied by clinical improvement manifested by improved color, easier respiration and slowing of the pulse rate.

It is imperative that accurate records be kept of the vital signs, all medications, intravascular fluids and oxygen therapy. Carefully kept records make possible an accurate evalua-

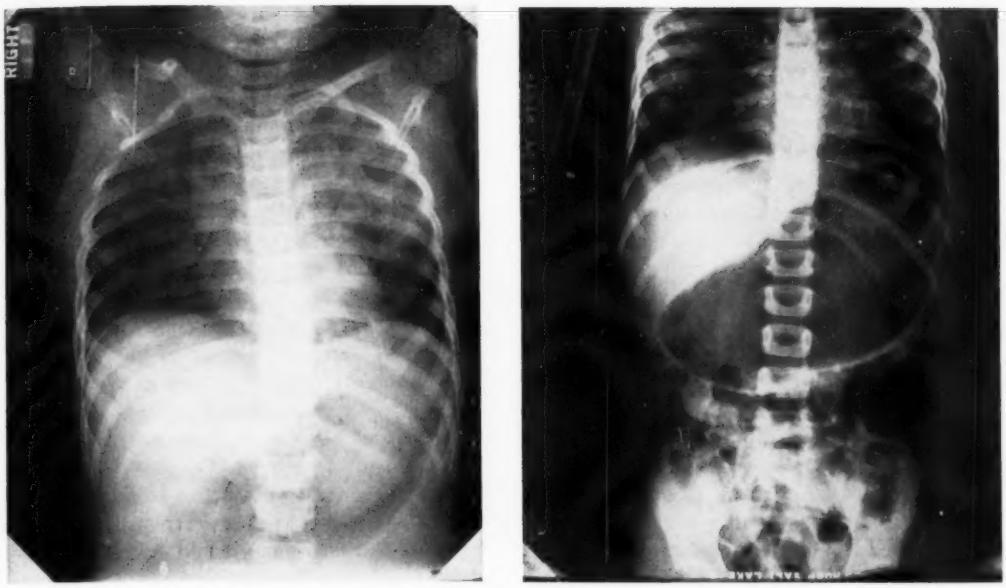

FIGURE 1. Roentgenograms of patients with admission diagnosis of probable ruptured spleen, showing marked dilation of the stomach. a *(left)*. Four year old female. b *(right)*. Six year old male.

(Reproduced courtesy of Drs. V. L. Stevenson and Emery M. Argyle, Dr. W. H. Groves Latter-day Saints Hospital, Salt Lake City, Utah.)

tion of the patient's condition at any particular time. Whenever patients are transferred to other institutions and personnel, it is important that a copy of such records be forwarded with them.

Problems Associated with the Gastrointestinal Tract

The aspiration of regurgitated gastric contents during induction, maintenance or emergence from general anesthesia is an ever-present hazard. This danger is particularly great in the recently injured patient. When pain, hemorrhage or emotional upset has been sustained, the motility of the gastrointestinal tract is markedly diminished. Food ingested prior to injury may be retained in the stomach for 18 hours or longer. If general anesthesia is contemplated, it is advisable to empty the stomach before the induction of anesthesia. Probably the simplest and most effective means of emptying the stomach is to induce vomiting by stimulating the gag and vomiting reflexes by the insertion of a gavage tube. Although liquid stomach contents usually can be aspirated through such a tube, solid food particles may remain in the stomach. The use of an endotracheal tube with inflatable cuff may serve to prevent aspiration of regurgitated stomach contents. The administration of oral fluids or solids to patients in whom general anesthesia is contemplated should not be permitted. Fluid, electrolyte or caloric requirements are best administered by the parenteral route.

Acute reflex gastric dilatation occurring after injury may result in cardiorespiratory distress. Pressure on the diaphragm and heart and possibly autonomic reflex mechanisms caused by the markedly distended stomach may produce deleterious effects on cardiorespiratory functions. Although this condition is not of frequent occurrence, its prompt recognition and treatment are important.

Acute gastric dilatation is illustrated in figures 1a and b. Although these patients presented a clinical picture of an acute condition of the abdomen, decompression of the stomach by means of a gastric tube promptly relieved the distressing symptoms. Both patients

made an uneventful recovery without surgical intervention. Leigh and Belton[1] have previously pointed out the significance of air-swallowing in crying children.

Management of Pain

Relief from pain in the recently traumatized patient is an urgent problem, except in cases of the severely injured where pain perception is markedly dulled. When pain is present, narcotics should be used judiciously and only in dosages sufficient to control the pain without harmful effects on the vital functions. In cases where peripheral circulation is depressed as a result of compensatory vasoconstriction, intravenous administration is the safest, since the effect is prompt and overdosage is less apt to occur. It is important to remember that drugs administered by this route should always be well diluted to a volume of 5 or 10 cc. and given slowly over a period of at least five minutes. Narcotics must be used with caution in patients with craniocerebral or thoracic trauma. These patients frequently experience hypoxia, and the injudicious administration of narcotics may mask symptoms or result in further respiratory depression which can be rapidly fatal.

Anxiety or fear accompanying trauma can often be effectively treated by convincing reassurance and the intravenous administration of a small dose of a short-acting barbiturate, such as pentobarbital sodium.

Restlessness, commonly associated with severe trauma, is frequently a symptom of hypoxia resulting from diminished blood volume. This symptom may often be relieved by oxygen therapy but is most effectively treated by measures designed to restore the blood volume.

Anesthetic Management

After the patient's response to resuscitative therapy has progressed to the point of meeting certain minimum criteria, anesthesia and surgery may be undertaken. The minimal criteria recommended are as follows: (1) a rising systolic blood pressure between 90 and 100 mm. Hg, (2) stability of blood pressure when the patient is moved, (3) a pulse rate of less than 120 per minute, and (4) dry and warm skin. A urinary output of 30 cc. or more per hour and the utilization of the tilt test have been suggested by Artz and Howard.[2]

Since anesthesia and surgery will cause additional stress to already taxed homeostatic mechanisms, it is vitally important to continue supportive therapy. Such measures may have to be continued well into the postoperative period.

Preanesthetic medication—Preanesthetic medication must be individualized. When shock or respiratory distress is not a problem and no other contraindications exist, narcotics may be used in moderate dosage. The belladonna drugs, such as atropine or scopolamine, are indicated in adequate dosage in conjunction with general anesthetics to suppress the flow of mucus in the respiratory tract and to protect against undesirable vagal reflexes. The short-acting barbiturates are useful to allay anxiety or fear. It is frequently advantageous to administer them intravenously.

Local and regional anesthesia—Whenever possible, local or regional anesthesia should be used. Of the various methods of anesthesia available, they interfere the least with physiologic processes. Often, because of the extensive nature of the surgical procedure or the inexperience of the operator, these methods are not feasible.

Spinal anesthesia—Experience gained during wartime indicates that spinal anesthesia is not well tolerated by patients recovering from hemorrhagic shock.[3] In patients suffering trauma not associated with diminished blood volume, spinal anesthesia is a useful technic and offers protection against the hazard of aspiration of gastric contents.

Intravenous anesthesia—Intravenous anesthetics such as PENTOTHAL® sodium are useful, nonflammable agents. They are commonly used to provide smooth, rapid and pleasant induction or as a supplement to other anesthetic agents. Experience indicates that these agents are best reserved for surgical procedures of short duration and for good-risk patients.

Inhalation anesthesia—Of the various inhalation agents available, nitrous oxide and

ethylene have very little disturbing effect on compensatory physiologic mechanisms. However, since these agents are relatively impotent, the high oxygen concentrations which are desirable for severely traumatized patients cannot be provided.

Both ether and cyclopropane, by virtue of their potency, can be administered in anesthetic concentrations in an atmosphere of high oxygen content. Ether was used extensively in military medical installations during World War II and was found to be well tolerated. Cyclopropane appears to have a decidedly beneficial effect on the circulatory system by its direct cardiotonic effect and minimal disturbances of compensatory vascular reflexes.[4-6]

Muscle relaxants—In surgical procedures requiring good muscular relaxation, the safety of the patient can be increased by the judicious use of muscle relaxant drugs. These drugs, while apparently possessing no anesthetic qualities of their own, permit an excellent degree of muscle relaxation under light planes of anesthesia, thereby avoiding the deleterious effects of deep planes of anesthesia.

In the selection of any anesthetic agent or technic, it is important to remember that the safety of the patient is directly proportional to the skill, experience and judgment of the anesthetist, regardless of the drug or method employed. For this reason, it would seem to be good judgment for the administrator to use the agent and technic with which he has the greatest skill and the most experience in similar circumstances.

Summary

The preanesthetic evaluation of the traumatized patient is based on history, physical examination and appraisal of the degree of shock present. Adequate preoperative preparation is essential for successful surgery. Surgery cannot be safely undertaken until the vital signs meet certain minimal criteria. Supportive therapy must continue throughout the operative period to combat the effects of anesthesia, surgical trauma and blood loss. The skill, experience and judgment of the anesthetist are as important as the choice of the anesthetic agent and technic.

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Postgraduate Clinical NOTES

41. STAIR ACCIDENTS

Actually, if you count only deaths caused by falls—and if you count all types of falls, at home and at work—the proportion of accidents occurring on stairways is a lot higher than those basic figures (12 of every 100 falls take place on stairways) would indicate.

Estimates by the American Society of Safety Engineers say that 17 per cent of all disabling accidents in industrial plants involve falls. They say that 12 per cent of all falls happen on stairways.

In the main working ages (25-64), stairway accidents account for about 35 per cent of the deaths caused by falls.

Occupational Hazards, March 1955, page 27

CLINICOPATHOLOGIC CONFERENCE

Report from Veterans Administration Hospital, Hines, Illinois

Report of Case*

A 56 year old white man was admitted to the hospital on January 13 for treatment of possible uremia.

(The resident on the Admission Service found little or no evidence of organic disease and suggested that the patient be seen by a psychiatrist. The psychiatrist, however, showed keen clinical judgment and suggested nonprotein nitrogen and blood sugar determinations. On the basis of an elevated nonprotein nitrogen thus found, the patient was admitted to the Medical Service.)

The patient stated that he had experienced a three day period of unconsciousness about a week prior to admission. He had been well all his life until that day, when, after coming home from work, he fainted and could not recall anything until three days later. When he awakened he was weak but did not have any aches or pains. He was told that during unconsciousness he did not have convulsions or episodes of disorientation, was not violent, and presented no particular symptoms except that he vomited frequently. Since the episode, he had lost his memory for recent events. He did not have other complaints such as headache, sore throat, difficulty in swallowing, chest pain, cough, expectoration, dyspnea, ankle edema, pain on walking, pain in the cardiac region, loss of appetite, indigestion, abnormal stools, or genitourinary or any other signs or symptoms.

(Thus we see that this patient had a period of unconsciousness, without convulsions or other manifestations except vomiting. These are the two essential features of the present illness.)

At the age of 22 years, the patient had an attack of gallbladder colic which was treated medically with success. He had typhoid fever in childhood. Appendectomy was performed in 1923. He had an operation on the left knee in 1916 for a "floating cartilage." Since 1942, pain and weakness in the left knee returned periodically. Otherwise, he had worked every day and had not been sick. His alcohol intake was about six to seven glasses of beer a day. He smoked about 20 cigarettes daily.

His father died of diabetes at the age of 63, and his mother died of tetanus infection. One sister died of diabetes at the age of over 50, and another died of "brain fever" in childhood. One brother died of "cancer of the brain." Beyond that, the patient's past history was not contributory. He worked as a crate maker in a stove factory.

*Interspersed through the protocol are some editorial remarks and bits of information found in doctors' and nurses' notes and laboratory reports which were omitted and should have been included for clarity and completeness. This material is in parentheses.

(The past history is entirely noncontributory and unimportant except that two members of his family apparently had severe diabetes, recognized clinically and so treated. The patient's occupation probably did not expose him to any toxic substances.)

Physical examination revealed a well-developed, well-nourished white man who appeared to be his stated age (56). He was cooperative and alert and appeared oriented in all phases. Temperature was 98° F., blood pressure 150/86, and pulse 80. (This blood pressure reading was the highest. Subsequent recordings were all normal.) The pupils were round, regular and equal and reacted to light and accommodation. The sclerae were slightly icteric. EOM and visual fields were normal. (I might mention that the psychiatrist did a funduscopic examination and found some tortuosity of the main arteries and slight A.V. nicking. The fundi were apparently otherwise normal.) The pharynx was not injected. There were no ulcerations on the buccal surfaces. The chest was not deformed. Breath sounds were diminished on both sides but of good quality. Rales were not found, and the diaphragm descended fully and equally on both sides. Tactile fremitus was normal. The heart was not enlarged to percussion. Tones were clear and strong and there were no murmurs.

Abdominal examination gave negative results, with no masses or palpable organs. A right paramedian scar was well healed. The right lobe of the prostate was slightly enlarged. Both lobes were smooth and not hard. There were no nodules. The right knee joint was slightly enlarged due to a bony enlargement of the medial aspect of the tibia. There was no limitation of this knee or of any joint. The joints were not tender or swollen.

Tendon reflexes were present and normal. (The psychiatrist noted hyperactivity of the deep reflexes with no pathologic reflexes.) There was no abnormality in sensation, muscle strength, gait, station, balance or co-ordination.

The skin was normal. A few shotty lymph glands were felt in the inguinal region, but axillary, cervical or epitrochlear glands were not palpated.

Urinalysis on January 14 revealed a trace of albumin, a few white cells, a few red cells and occasional casts, but no acetone. Nonprotein nitrogen was 115 mg. per cent, creatinin 5.6 mg. per cent, sugar 104 mg. per cent and cholesterol 144. Serologic tests were negative. The stool did not contain occult blood. Blood count showed the following: red blood cells 5,000,000; hemoglobin 14.5 gm.; white blood cells 12,500 with 71 per cent neutrophils, 28 per cent lymphocytes and 1 eosinophil. Liver function tests gave results within normal limits. Chest x-ray negative. An electrocardiogram was normal.

The patient was seen by consultants in the Psychiatry Section. Their opinion was that the patient had arteriosclerosis with nonpsychotic reaction. Examination of spinal fluid gave normal findings. The blood pressure was taken at frequent intervals and at all times was normal. Concentration and dilution tests were done, and the specific gravity of the urine ranged from 1.010 to 1.020. (The latter figure is slightly misleading, as I will show you shortly on a summary chart.) The phenolsulfonphthalein excretion was 20 per cent in 15 minutes.

During the first few weeks in the hospital, the patient did not have any complaints except that he vomited occasionally. However, his fluid intake and output were considered adequate. (These were not measured, however.) Further examination of the blood showed a nonprotein nitrogen content of 101, a blood urea nitrogen of 72.5 and a creatinine of 8.1 on January 23. Although there was no change in the patient's behavior, the nonprotein nitrogen was 159 mg. per cent and the creatinine 5.7 on January 30. He was seen in consultation by the Urology Department. No genitourinary abnormality was found to explain the high nonprotein nitrogen.

Intravenous pyelography showed poor excretion of dye but adequate excretion of indigo carmine. During frequent interviews, no pertinent facts in the patient's history were discovered. However, the patient's wife stated that at one time (we have no indication as to how far back this occurred) he had ulcers. Therefore, a gastrointestinal series was or-

dered. An x-ray showed a stenosing lesion of the pyloric region of the stomach. Another check of the blood chemistry showed a nonprotein nitrogen of 44 mg. per cent and a creatinine 2.6 mg. per cent on February 9. (These isolated low readings are confusing, when all preceding and subsequent determinations were very high.) About that day, the patient began to vomit a great deal, but blood was not noted. He was given adequate amounts of intravenous fluids.

On February 11, he stated that he had not urinated for two days, and he was therefore catheterized; 450 cc. of clear urine was obtained with a specific gravity of 1.012, 1 plus albumin, and 1 plus sugar. (This may have been shortly after an intravenous injection of glucose, and I do not think the finding of sugar in the urine was significant because he did not have acetone bodies or other evidence of acidosis.) On that day, nonprotein nitrogen was 88, and creatinine 6.7 mg. per cent. On February 12 the values were: fasting sugar 143, creatinine 8.7, nonprotein nitrogen 125 mg. per cent, carbon dioxide-combining power 116 vol. per cent. (One previous determination of the latter, not mentioned in the protocol, was 60. That was about six days prior to this last one.) It was felt that the patient had a stenosing lesion of the pyloric end of the stomach, thus losing large amounts of chloride through vomiting. He was therefore given large amounts of saline and glucose intravenously.

(The term "large" is misleading. The patient had vomited up to 6000 cc. on one day and received only 2000 cc. of fluid intravenously, and only 1000 cc. of this was saline.)

On the morning of February 12 the patient had Cheyne-Stokes respiration. He did not regain consciousness and died at 2:35 P.M. on that day.

I might add (this is not given in the protocol) that about six days before he died, because he complained of gastric distress, the patient was started on alkalis by mouth. Rhubarb and soda or soda alone was ordered. From that day until he died, a period of five days, he received 13 or 14 doses of rhubarb and soda or straight soda. This no doubt contributed to the marked alkalosis which he had terminally.

Another point not in the protocol is that on February 10 the patient had a seizure of short duration which was characterized by generalized muscular twitches. The medical night resident saw the patient and found nothing focal, and the episode passed without further incident.

Differential Diagnosis

It is very difficult to get a bird's-eye view of this case by just reading the protocol. The many clinical and laboratory factors have therefore been condensed on the accompanying chart. This will recapitulate the clinical course and laboratory findings and help emphasize the important points graphically.

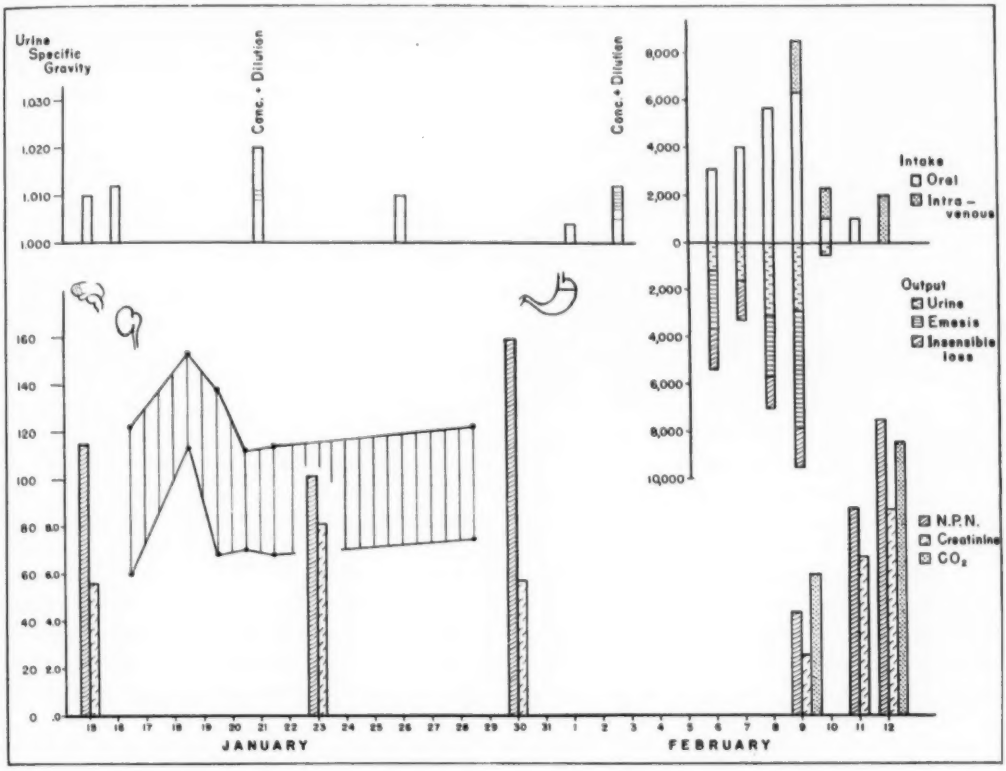
This chart indicates that the patient was admitted with a history which suggested cerebral disease, possibly with frontal lobe involvement. The finding of an elevated nonprotein nitrogen focused immediate attention on the renal factor which was further studied on the Medical Service.

Blood chemistry indicated early uremia. Blood nonprotein nitrogen values were 115, 101, 159, 44, 88 and 125 on January 14, 23 and 30, and February 9, 11 and 12, respectively. Creatinine values were 5.6, 8.1, 5.7, 2.6, 6.7 and 8.7 on the same dates. The low values on February 9 are difficult to explain.

The patient's blood pressure was practically normal during this period except on January 18 when it was 150/86. Subsequent readings were all about 120 systolic and 80 diastolic.

A check of his renal function by means of the specific gravity test, illustrated in the left upper portion of the chart, showed consistent concentration between 1.010 and 1.012. Two concentration and dilution tests also showed fixation at about 1.010 with only one determination at 1.020. The latter single determination above 1.012, as I said previously, may be misleading. Thus far the evidence indicates impairment of the renal secretory and renal absorbing mechanism.

We see, too, that signs of gastric disturbance great enough to be noted made their appearance during the third week. This disturb-



ance was manifested by intermittent vomiting and gastric distress. The X-ray Department observed a large amount of retained fluid in the stomach when barium was given. It also reported an obstruction at the pyloric end of the stomach.

The probable relationship between the gastric disturbance and the impaired renal function is demonstrated in the right upper half of the chart. Quantitative measurement of the intake and output was first made on February 6 and was continued for the week before the patient died.

On first glance it would appear that the urinary output, which ranged between 1200 and 3000 cc., was quite adequate. However, with the specific gravity fixed near 1.010, this urinary output would not suffice for elimination of the nitrogenous elements. The oral intake, ranging between 3000 and 6000 cc., similarly appears adequate. However, balanced against the great quantities lost by vomiting and the insensible loss, it is inadequate. One can easily see on the chart that the bars representing total output are all longer than those representing total intake.

Finally, attention is again called to the terminal high value of the carbon dioxide-combining power, 116 vol. per cent. This may have been due in part to the alkali which the patient was receiving, and to compensatory alkalosis resulting from a marked hypochloremia. This point is not subject to proof without a concomitant chloride determination.

Essentially, then, we have a patient who came to this hospital for what appeared to be a cerebral disturbance. He was found to have uremia and evidence of impaired renal function. In addition, signs of pyloric obstruction, alkalosis and tetany developed, and he finally

died. The problem now is to decide on the patient's primary disease and the cause of his death.

Consider first the patient's coma. It may have been caused by intrinsic cerebral disease or by systemic diseases, secondarily affecting the cerebrum.

We think of the following conditions in the first group: (1) Hemorrhage into a previously silent frontal lobe tumor may cause coma with few if any localizing signs; (2) a chronic subdural hematoma may cause mild personality changes, vague memory defect and finally coma with no localizing signs; (3) thrombosis or embolism in arteriosclerotic disease gives focal signs because the internal capsule or an active area in the cortex is usually involved. This patient, however, had no signs of increased intracranial pressure, his fundi were normal, his spinal fluid was normal in dynamics, and it contained no abnormal cells. Also, he recovered spontaneously from the coma and it did not recur. The evidence therefore rules out a localized organic lesion of the cerebrum.

The commoner extrinsic causes of coma are alcohol, diabetes, poison or uremia. Apparently the patient's alcoholic intake was moderate and included only beer. Whether the episode of coma was an alcoholic stupor we cannot say. With a history of diabetes in two immediate members of the family, diabetic coma should be considered. However, there is no supporting evidence for diabetes. At no time did he show clinical acidosis, elevated blood sugar, persistent glycosuria or chemical findings of acidosis. There is no evidence that he ingested any toxic substance, nor was he exposed to any in his occupation.

This leaves the last possibility, uremia, for which the evidence already has been presented. We can set up three possible sites in regard to the etiology of the uremia: postrenal, renal and prerenal.

Postrenal uremia is caused by obstruction to the flow of urine already formed. To have bilateral renal pelvic or ureteral obstruction is hardly likely. A large bladder stone rarely obstructs both ureters. A bladder tumor in the vesical neck or trigonal area may cause complete obstruction, renal damage and uremia. Cystoscopic and retrograde studies ruled these out. The prostate similarly could not be incriminated from the clinical and cystoscopic evidence.

Renal uremia commonly is caused by chronic nephritis, arteriosclerosis, nephrosclerosis (arteriosclerosis), polycystic disease and amyloid disease.

It is not likely that this patient had chronic nephritis. He was not in the age group in which this disease is most common, and he did not have hypertension, cardiac enlargement or fundic changes. For the same reasons, arteriosclerosis (essential hypertension) is ruled out.

In nephrosclerosis, arteriosclerosis of the renal vessels causes localized areas of ischemia, atrophy and fibrosis of the secreting and absorbing elements. Usually enough functional tissue remains to carry on normal function, though with limited reserve. This condition may, however, continue until loss of kidney substance leads to uremia without hypertension, cardiac enlargement or changes in the eyegrounds.

Polycystic disease probably would have shown up much earlier in this man's life. Renal bleeding is often a prominent feature, and progressive destruction of the renal parenchyma often does lead to chronic uremia, hypertension and cardiac enlargement. Amyloid disease is mentioned only in passing. There was no obvious cause for an amyloidosis of the kidneys in this case.

Prerenal uremia, and perhaps here we had better use the term azotemia, is caused by an excess production of nonprotein nitrogenous elements or a deficient elimination of these elements produced in normal quantity.

Following an extensive gastrointestinal hemorrhage, digestion of blood in the alimentary tract produces large quantities of nitrogenous waste products which cannot be excreted, even by a normal kidney, as rapidly as they are produced. This patient's original period of unconsciousness is not likely to have been due to gastrointestinal bleeding. The coma lasted too long, and there was no associated hematemesis or melena. Then, too, the

azotemia is transient and disappears soon after the blood is passed out of the gastrointestinal tract. In this case it persisted.

Deficient elimination of nitrogenous elements is caused by depressed kidney function when water and electrolytes are not supplied to the kidney in sufficient quantity. This may be by excess loss (as in vomiting or high fistula), by inadequate intake or by a combination of both. The evidence on the chart indicates that both factors were operating here. However, one cannot state with complete assurance that this patient's uremia was entirely due to the prerenal factor. An element of organic renal disease was surely present as shown by the fairly fixed specific gravity. A kidney with adequate reserve probably would have put out less urine but would have concentrated to a specific gravity of 1.025 or 1.030 in the presence of the fluid deficiency shown.

It should be pointed out here, too, that both advanced renal disease and pyloric obstruction with vomiting finally produce a very similar picture. The following table makes this clear.

Advanced renal disease	*Pyloric obstruction with vomiting*
Acid accumulation in blood (phosphate and sulfate retention)	Acid loss by vomiting (chloride)
Acidosis	Alkalosis
Nitrogen retention	Nitrogen retention
Calcium reduction	Calcium reduction
Twitchings and convulsions	Tetany

The last factor warranting discussion is the cause of the patient's vomiting, the pyloric obstruction. The patient had a history of ulcer, and x-ray showed great retention of fluid and obstruction at the pyloric outlet. However, the x-ray reading did not indicate whether the obstruction was caused by an ulcer or by malignancy. A benign ulcer with stenosis is not unlikely in this case. However, the patient's age (56 years), the absence of a recent history of ulcer symptoms or obstruction, and a weight loss of 20 lb. make the presumptive diagnosis of gastric malignancy more likely.

The clinical diagnosis may be formulated as follows: The patient probably had moderate nephrosclerosis with adequate renal function under normal circumstances. He was thrown into renal failure and uremia with the tremendous fluid and electrolyte loss consequent to pyloric obstruction. The latter was most probably due to a carcinoma in the pyloric region of the stomach.

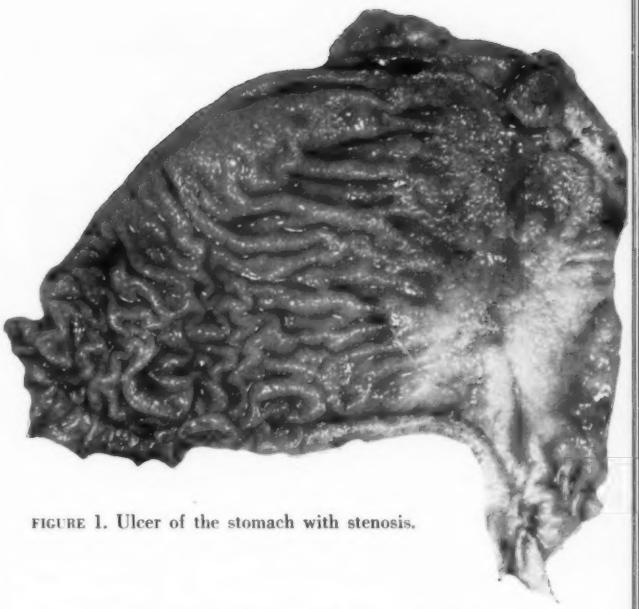


FIGURE 1. Ulcer of the stomach with stenosis.

Postmortem Examination

DR. WILLIAM BENNER: Examination of the brain did not reveal gross evidence of hemorrhage or other abnormality externally or on multiple transverse sections. On removing the dura, a marked degree of edema was noted in the piarachnoid.

The combined weight of the kidneys was 310 gm. The cortex and medulla in each were healthy in color and the markings preserved. There were several cortical cysts in the left kidney, 1 to 3 cm. in diameter. The kidney pelves, ureters, bladder and prostate were normal. Microscopically, the glomerular and tubular structures were well preserved. A moderate degree of arteriosclerosis involved the medium and large arteries.

The stomach was markedly dilated, particularly its proximal half. The distal portion was somewhat contracted and sausage-shaped. In the pyloric ring was a firm fibrous area which was bound down to the surrounding tissues. Within the stomach, just proximal to the pyloric ring, was an ulcerated area with sharply

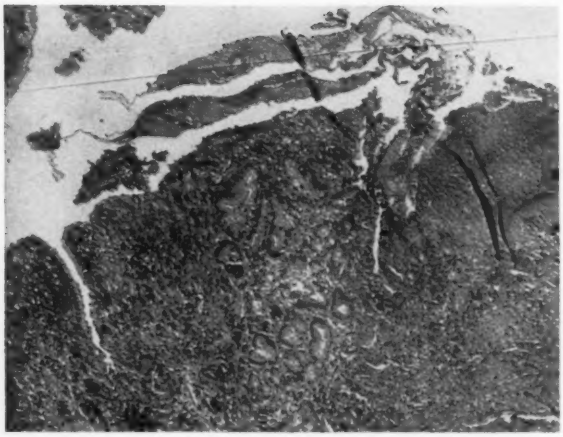


FIGURE 2. Low power microsection of base of ulcer.

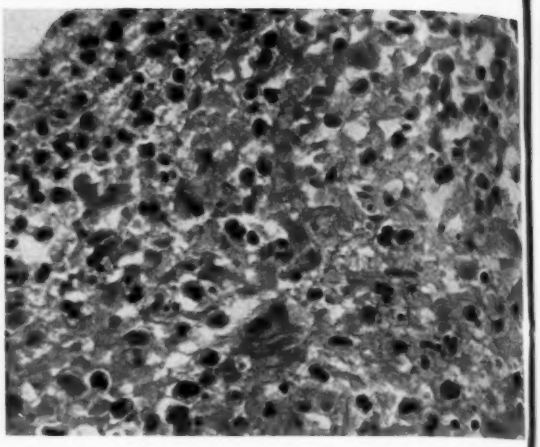


FIGURE 3. High power microsection of base of ulcer.

punched-out borders 1.2 cm. in diameter and 1 cm. deep, whose base was the capsule of the pancreas. The pyloric ring was just distal to this ulcer and was greatly narrowed so that even with stretching it appeared to be only about 5 mm. in diameter. Microscopic examination confirmed the gross diagnosis of benign prepyloric ulcer.

Anatomic Diagnosis

1. Chronic prepyloric ulcer with severe stenosis of the pyloric ring.
2. Coronary and generalized arteriosclerosis.
3. Cerebral edema.

Discussion

A clinicopathologic conference not only should challenge the analytic powers of the discusser and his ability to arrive at a correct diagnosis, but, more importantly, should provide a forum where we can examine our results critically, learn our weak points, and thus improve our diagnostic and therapeutic care.

To fulfill this latter function, let us examine where we went astray in this case. After the original diagnosis is made, an inertia develops which dulls our imagination. We therefore neglect to explore other possibilities, and our therapy tends to follow the original pattern too. In this case, it seems that the diagnosis of uremia on the basis of renal damage was made, and the patient's vomiting accepted as a part of the uremic picture. As a result, too little attention was paid to the x-ray finding of pyloric obstruction and to the quantitative aspects of the patient's fluid loss. In retrospect, it is clear that intubation and continuous gastric aspiration should have been carried out. This not only would have relieved the gastric dilatation and possibly even the pyloric obstruction, but also would have given an exact quantitative measure of the fluid loss.

Then, too, the "inertia" following our original diagnosis led to neglect of certain aspects of chemical analysis. While 15 or more determinations were made of the nonprotein nitrogen elements in the blood, only one chloride and two carbon dioxide-combining power determinations were done. This in turn led to neglect of proper fluid and electrolyte replacement therapy which probably was the keystone in this case.

An important and helpful aid in overcoming this inertia is to get a graphic picture of a case in which certain features are puzzling or do not seem to fall into a pattern. This is easily done by drawing up what the engineers call a "flow sheet," which is simply a diagrammatic representation of a sequence of events and processes. The accompanying chart is such a flow sheet and helped immeasurably in clarifying this case.

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THE PLAYTEX PARK RESEARCH INSTITUTE

Among the many foundations which have been established to provide funds for medical research, the Playtex Park Research Institute is unique. In 1950 the International Latex Corporation set up a fund to aid pediatric research and education. Since that time about $750,000 has been given through more than 50 grants-in-aid to support investigations in hospitals and universities. The Institute is governed by a board of 25 members, almost all pediatricians, and its executive committee under chairman Dr. Charles F. McKhann, Jefferson Medical College, Philadelphia, includes Dr. Joseph Stokes, Jr., University of Pennsylvania; Dr. Sidney Farber, Harvard University; Dr. W. C. Davison, Duke University; Dr. J. L. Wilson, University of Michigan; and Leona Baumgartner, Commissioner of Health of New York City.

A survey of the publications reporting results of investigations made under grants from the Institute indicates that the contributions have added greatly to basic scientific knowledge, particularly in the biochemical approach to problems of disease in infancy. A number of researches, however, have dealt with applied knowledge on such subjects as viral hepatitis, kidney function, suture material used in vascular anastomoses, use of various antibiotics, and prediction of premature birth. One recent report made from the University of Colorado describes a low level of estrogen excretion and early abnormal activity of the uterus as pointing toward premature birth. This report indicates that as early as the twenty-sixth gestational week the uteri of those patients studied who delivered prematurely were excessively irritable.

The grants-in-aid technic for supporting research is now the usual method by which most foundations distribute funds. Obviously the quality of any program is largely dependent on the committees which study applications for aid to determine their merit. The decisions of the 25 governors of the Playtex Park Research Institute have yielded progress in a special field in which basic studies are especially important.

MORRIS FISHBEIN

MENTAL DISORDERS IN THE UNITED STATES

SINCE 1935 the number of first admissions to hospitals for the long-term care of patients with psychiatric disease has increased over 60 per cent. Nearly 40 per cent of the total bed capacity of hospitals in the United States is required for the care of patients with mental illnesses and another 10 per cent for epileptics and mentally defective children. The statisticians are careful to explain that some of the rise is due to the increase in population and the increase of older people in the population.[1]

An exhibit on "Mental disorders in the United States" by Drs. William P. Shepard, Earl C. Bonnet and Herbert H. Marks, displayed in the Scientific Exhibit at the annual session of the American Medical Association, brilliantly emphasized the incidence of mental disorders, the prognosis and the community needs. Some facts stand out in bold bas-relief:

About one in four workers has mental or emotional difficulties sufficient to interfere with well-being and productivity. Only a fraction are recognized as psychiatric cases.

The upper social group has the highest rate for neuroses, but the lowest for psychoses.

The increase has been greatest for mental disorders associated with aging. First admissions for disorders due to syphilis have declined sharply.

. . . the experience gives indication that the majority of persons with breakdown due to neuroses make satisfactory life adjustments.

What delays our progress in the campaign to control mental disease?

1. Social stigma attached to the disease in the family and the consequent reluctance to admit its existence.

2. Feeling of hopelessness about the possibility of cure.

3. Lack of recognition of the necessity for treatment.

4. Lack of medical personnel and facilities for treatment.

More and better-trained personnel provided with more and better facilities are required. Research should be adequately supported as it is now for cancer, heart disease, tuberculosis and poliomyelitis. And in these conditions, as in many others, treatment must be followed by total rehabilitation.

Progress resulting from research has already yielded notable victories in the field of mental disease. Biochemistry, physics, nutrition and drug therapy, as well as purely psychiatric knowledge, are being applied for investigation, diagnosis, prevention and treatment of mental disorders to which formerly the only approach was domiciliary care under controlled conditions. The results are a constant stimulus to further effort. But education of the public and of adequate numbers of professional personnel still remains the major need if further progress is to be made rapidly.

MORRIS FISHBEIN

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1. The Outlook for Mental Patients. Statist. Bull. Metrop. Life Insur. Co. 36:1 (April) 1955.

CLINICAL TRIALS OF GASTRIC ULCER TREATMENTS

IN Great Britain, under the Medical Research Council, studies have been made for the past seven years on the rate of healing of gastric ulcers. An earlier report showed that a faster rate of healing was obtained with treatment in bed in a hospital than it was with ambulant treatment. The previous study found also that effects could not be attributed to the routine administration of phenobarbital or of ascorbic acid. Now another series of studies[1] has been completed using continuous intragastric milk drip, using a tissue extract called ROBADEN® and using cabbage juice. The treatments were varied for control purposes to include Robaden and cabbage juice, Robaden alone, cabbage juice alone, and neither Robaden nor cabbage juice. All patients were kept in bed for four weeks on a basic diet. After the fourth week a convalescent gastric diet was substituted. When requested by the patient for the relief of pain, the usual alkaline powder was prescribed. Half the patients in each treatment group were given six pints of milk every 24 hours as a continuous intragastric drip for

two weeks, followed by two pints of milk by drip throughout the night for 10 days.

Cheney recommended cabbage juice first in 1950 claiming that it contained a factor, which he called vitamin U, capable of preventing the development of histamine-induced ulcers in guinea pigs. In the British experiments 24 patients were given cabbage juice and 24 were not given cabbage juice. The results seem to have been essentially negative. In 11 patients in each group the ulcer niche diminished in size by two-thirds or more in one month. The authors say that it is possible that the discrepancy between these results and Cheney's arises from the use of insufficiently fresh cabbage or of a different type of cabbage.

The product called Robaden is a proprietary preparation of gastric and intestinal tissue extract which was found experimentally to protect rats, in which the pylorus had been ligated, against the development of gastric ulcers and to prevent guinea pigs from developing histamine-induced ulcers. The extracts are protein-free and therefore chemically distinct from enterogastrone.

Almost a dozen investigators reported that results obtained with Robaden were better than those obtained without it, although some investigators have already reported that they were unable to confirm this benefit. The British investigators now find that they had to stop treatment in some cases because of persistent pain in a greater proportion of patients given Robaden than in the control patients. The effects of Robaden on the healing of gastric ulcers were assessed by comparing the results obtained in 32 hospital patients with a control group of 32 patients and by studying 100 outpatients observed for one year, half of whom were given Robaden while the other half were given inert preparations of similar appearance. The investigators did not find any definite effects resulting from the use of Robaden, and they say that it does not influence the healing of gastric ulcers.

MORRIS FISHBEIN

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CHILD PSYCHIATRY

Most popular among subjects for conversation where both the *hoi polloi* and the intelligentsia gather in these hectic days are the problems of children. Are the movies responsible for juvenile delinquency? Is it good for children to go through epidemics of admiration for the Lone Ranger, Hopalong Cassidy and Davy Crockett? Was it always thus or is there a new breed of juveniles?

In her chairman's address to the Royal Medico-Psychological Association in 1953, Dr. Mildred Creak[1] noted that Tacitus wrote during the days of the Roman Empire:

"The children are now put in charge of a Greek nursemaid, with a couple of slaves of low type to help, whose tales are attractive but coarse. . . . The children's minds are now full of acting, gladiators and horse racing; for what else does one now hear talked about in a household?"

Dr. Creak also observed that in the old days the great fight was to preserve the lives of the infants and children. In England in the middle of the eighteenth century more than half the children died before they were two years old. Combe reported that in Manchester in 1844, 3600 children annually were found straying because their mothers were working.

Society today is groping for answers which are not readily apparent to meet the problems of children and adolescents. Putting the blame on television, comic books, movies, working mothers or broken homes does not explain the cases of delinquents who have homes that are serene and affectionate, of those who have no television sets, or of those whose mothers are so much with them that they are charged with overprotection.

Most physicians will agree with Dr. Creak that there is no expert method with guaranteed results for meeting this situation. Research has not found either a specific cause or a certain method of cure. About all that she has to suggest is emphasis on loving-kindness and tenderness.

"The quality of love, which is essential in good parents, begins with love of the pair for

each other, and with love of the idea of having children—not in order to justify marriage, or even to cement its bonds, but as part of the job as a whole. Children who are the natural outcome of love will be loved as much when they are bad as when they are good (or even a little more)."

The psychiatrists are apparently convinced that "a conflictless and suffering-free childhood" would solve many problems. This is purely an assumption and evidence is lacking that such a childhood is possible under any system—communal, familial or vagrant. Indeed, society seems to be fortunate that so many children turn out well under any and every circumstance.

MORRIS FISHBEIN

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PSYCHOCUTANEOUS MEDICINE

Almost suddenly dermatologists have begun to concentrate on the obvious connection that prevails between the mental mechanisms and the skin; yet for many years dermatologic writings have noted the association. Perhaps most obvious have been the superstitions and folklore related to the disappearance of juvenile warts. Just how hypnosis or suggestion acts to remove infectious dermatoses such as warts or herpes simplex is not clear—but these technics are employed as a last refuge when other methods fail—and they succeed!

Another clear relationship is the appearance of allergic responses which fluctuate with a lowering of the threshold that accompanies emotional tension. More difficult to comprehend, as Obermayer[1] points out, is the replacement of a nondermatologic symptom, such as psychogenic chorea, by lichen simplex chronicus or by erythrophobia. The transfer, he suggests, is accomplished only if both the substituted and the original symptoms have the same neurotic significance.

For many years neurotic excoriations and factitial dermatitis have been related to emotional disturbances. The older dermatologists wrote: "The outcome depends upon the possibility of restoration of the nervous system to its normal condition." Nevertheless, they seldom called on the psychiatrist for aid in solving the problem. Lichen simplex chronicus was called neurodermatitis circumscripta and was thought by Wise to be associated with asthma and hay fever.

Obermayer now emphasizes the need for more research from the psychologic as well as neurophysiologic and biochemical approaches. He says:

"Perhaps the most important psychologic studies concern the psychodynamic mechanism of symptom formation. Until recently patients with the true dermatoneuroses—such as neurotic excoriations and factitial dermatitis—were labeled by dermatologists as 'hysterics.' Semantic distinction of the term hysteria long has been appreciated by psychiatrists, however. Persons with the psychoneurotic complex called hysteria characteristically avoid pain and never inflict severe damage on themselves. Patients who injure themselves severely must be considered psychotic. Nevertheless there is mounting evidence that most psychocutaneous symptoms may be the product of a psychotic mechanism (Macalpine); although this does not mean that persons with psychocutaneous symptoms are psychotic, their mechanism of cutaneous symptom formation may be identical with that which brings about a psychosis in a psychotic patient."

The teachers of dermatology have always noted that the skin is a mirror of the body. In urging joint experimental investigations by psychiatrists and dermatologists, Obermayer recalls a statement made frequently by Professor A. J. Carlson, of the University of Chicago: "Gentlemen," he would trumpet, "psychoanalysis has no laboratory." And now ventures Obermayer, "Perhaps dermatology can provide such a laboratory."

MORRIS FISHBEIN

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FIRST AID AND OCCUPATIONAL MEDICINE

A RECENT issue of *Occupational Hazards* is devoted to a four part study of planned medical programs—their costs, equipment, personnel, methods and results. The series begins with the following aphorism, "A sound medical program, supported by adequate plant dispensary and first-aid service, almost inevitably will make a profit for the employer."

A survey made by the President's Commission on the Health Needs of the Nation in 1950 indicates that for all industries medical services cost an average of $14.53 per worker each year. Allowing for a 50 per cent increase in this cost since 1950, it now comes to something around $21 per worker each year. This includes salaries of doctors, nurses and necessary clerks, record systems, supplies, light, heat and rent. The suggestion is made that for an ordinary plant, floor space of not less than 100 square feet should be allotted and, of course, for larger plants more floor space. The rooms should be well separated from working areas, have ample supplies of hot and cold running water and be equipped with electrical outlets. The rooms should be well heated and ventilated and the lighting should be excellent. Most important, however, is another aphorism: "Dispensary or first-aid rooms should never be used for anything other than the examination and the care of employees."

Obviously the selection of equipment for the dispensary or first-aid rooms should be left to the physician who is to utilize it; however, minimum equipment must include a wash basin, toilet, towel rack, container for paper cups, table or couch for examination and treatment, waste receptacle, desk, table, chairs, storage cabinets, and, obviously depending on the scope of the plant, a stretcher or treatment chair, screens, resuscitator, cabinet for drugs and perhaps even material for brief anesthesia. The list may, of course, extend to extra equipment such as roentgen ray machines, fluoroscopes, infrared lamps or diathermy apparatus. However, the ordinary small plant reasonably accessible to a hospital should not require that type of equipment. Various states have laws regulating the installation and equipment of dispensary or first-aid departments and some even go so far as to specify the content of the first-aid cabinet. California and New Hampshire list the following content: "The chest shall contain an adequate assortment of absorbent lint, absorbent cotton, sterilized gauze, plain and medicated, adhesive plaster, cotton and gauze bandages, one tourniquet, one pair of scissors, one pair tweezers, one jar carbolized petrolatum, one bottle antiseptic solution, and one first-aid manual, all of which shall cost not less than six dollars ($6.00)."

In Detroit the recommendation has been made that small first-aid kits be placed conveniently around the plant and that each first-aid kit supply the name and the telephone number of the ambulance to be called, hospital used for emergency cases, the plant doctor, and the person within the plant to whom injuries must be reported.

A special section of the report deals with the industrial nurse and with the tremendous increase in this type of personnel and their integration into the industrial plant. Actually, it is suggested that the nurse will be a safety engineer. She can be instrumental in determining especially hazardous occupations because she comes early into contact with the injuries developing from certain departments. She may promote the use of safety equipment, recognize the existence of industrial toxicology, and analyze the causes of absenteeism. Indeed, as is discussed in this interesting article, one must conceive of the industrial nurse as fulfilling most of the functions of sanitary officers in the armed forces.

The fourth part of the series is concerned with industrial hygiene and cites numerous examples of progress that has been made in this field during the last 10 years. The industrial hygienist may serve with the plant physician, the safety director and the industrial nurse to make a team which is responsible for preventing illnesses, accidents and industrial health problems. The plant housekeeping and sanitation, as well as the maintenance of health conditions in the restaurant or cafeteria, may

be primarily problems of the industrial hygienist. To him come problems of dangers from industrial gases, radiation, atmospheric pollution, and pollution of water supplies and the problems associated with jet sprays, cutting oils, adverse effects from microwaves, injuries to the eyes and many similar problems.

An interesting comment by Dr. Holle states, "For every employee who is absent because of illness, at least 12 others because of impaired health are merely going through the motions of doing something."

State health departments work in close relationship with industrial hygienists, and in many states there are laws specifying minimum standards which the hygienist must enforce.

The rise of occupational medicine as a specialty in medicine makes this series of articles of special significance to all general practitioners and indeed to all physicians who are confronted from time to time with the new medical problems that frequently arise in modern industry.

MORRIS FISHBEIN

JOSIAH MACY, JR. FOUNDATION 1930-1955

In April 1930 when the Macy Foundation was established, far more aid was being given to biochemical and physiologic research than to psychobiologic and sociologic questions. In her message establishing this foundation, Mrs. Walter Graeme Ladd, whose initial gift was $5,000,000, expressed the hope that the foundation would take more interest in the architecture of ideas than in the architecture of buildings and laboratories. Since that time Mrs. Ladd gave other gifts and on her death she left the foundation approximately $13,000,000. The present value of the endowment is in excess of $28,000,000.

During its first quarter century, the Macy Foundation has led in emphasizing the psychosomatic approach in medicine and in problems of aging and mental health. It has made many grants-in-aid for research in practically every field of the basic medical sciences and medicine. Its aid in establishing a new trend in research has been invaluable; perhaps this is expressed best in the following sentence by the current president of the foundation, Dr. Willard C. Rappleye: "There is today impressive evidence that the psychological influence of one individual upon another or upon a group is exerted through physiological and biochemical processes, and that the whole organism is involved in all interactions among people."

In the twenty-fifth anniversary report, special chapters are devoted to the activities of the Macy Foundation, conference groups which have met to discuss a great variety of subjects, and its work in national defense, in medical education, on the public health, on the life cycle and on the relationships of the individual to the group. A special section of the report, headed "Research and medicine," lists briefly the many grants-in-aid and the results that have been published. This listing includes many of the great names in medical research of the past quarter century and records the medical progress of that period.

The directors of the Macy Foundation chose wisely in the persons selected for aid and the funds granted have been most productive. The report just published is a fine document prefaced by a reproduction of the portrait of Kate Macy Ladd. An understanding of the content of the report should inspire all who work in this and similar fields and convince everyone of the significance of such private philanthropies in aiding and stabilizing the progress of scientific and medical research in the United States. The universities of our nation are "the sanctuary of scholarship and the natural habitat of basic research." There has been a true partnership between the Macy Foundation and the universities.

MORRIS FISHBEIN

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1. The Josiah Macy, Jr. Foundation 1930-1955: A Review of Activities. New York, Corlies, Macy & Company, Inc., 1955.

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1. Forsham, P. H., et al.: Paper presented at First Internat. Conf: on Prednisone and Prednisolone, New York, N. Y., May 31-June 1, 1955.

*brand of prednisolone

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THE MEDICAL Bookman

► DIAGNOSIS OF CONGENITAL HEART DISEASE

By Sven R. Kjellberg, Edgar Mannheimer, Ulf Rudhe and Bengt Jonsson, Karolinska Sjukhuset Pediatric Clinic, Stockholm. 649 pages with 581 illustrations. 1955, The Year Book Publishers, Inc., Chicago. $22.00.

The subject matter of this book was obtained under very favorable circumstances. Two cardiologists and two roentgenologists, working as a diagnostic team, studied a wealth of clinical material, with the best of modern equipment at their disposal. Most of their subjects were children, numbering almost 400. In addition to making a very careful appraisal of the clinical findings, this team utilized most of the modern investigative technics in this field, including cardiac catheterization, angiocardiography and electrokymography. Lesions studied included practically all of the congenital anomalies compatible with life beyond early infancy.

The earlier chapters are devoted to embryology, roentgenologic anatomy and physiology of the heart, and are followed by detailed descriptions of individual congenital anomalies. Technics of special examinations are described in detail, and the authors discuss very frankly the complications which might occur. They had only one fatality in 425 catheterizations, and only three in 340 angiocardiographs, all occurring in seriously sick children.

This book is especially commendable because the specific advantages of every type of special examination are defined in reference to each congenital anomaly. For example, the authors point out that catheterization is more reliable for the accurate diagnosis of pulmonic stenosis than are any other methods; they state that angiocardiography is superior in the evaluation of the tetralogy of Fallot. Angiocardiography, however, requires injection of the contrast medium directly into the right ventricle. When this procedure is done, the anatomic conditions in the outflow tract, the diameter, course and branches of the pulmonary artery, the overriding of the aorta and the degree of such overriding, and the anatomic relationships of the systemic arteries and their possible relationship to the pulmonary artery and its main branches are better defined. The authors outline many other specific details in the study of other anomalies.

The work reflected in this volume is a departure from the investigations of some workers who, because they have become especially adept at one particular type of investigation, have more or less ignored or neglected other means of studying the hemodynamics of the circulation.

Dye-dilution curves are not mentioned in the book. The volume is profusely illustrated with excellent photographs of gross specimens, roentgenograms, angiocardiographs, kymographs and other graphic presentations. The angiocardiographs, especially, are among the best that have ever been reproduced.

The text reads easily and the translator is to be commended. The book covers basic physiologic and anatomic material which is unlikely to become outdated for some years. It is highly recommended to physiologists, cardiologists, roentgenologists and the surgeon interested in cardiac surgery.

T. J. D.

(Continued on page A-114)

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► CARDIAC AUSCULTATION

By J. Scott Butterworth, M.D., Associate Professor of Medicine, Maurice R. Chassin, M.D., Assistant Professor of Clinical Medicine, and Robert McGrath, M.D., Associate Professor of Clinical Medicine, New York University Post-Graduate Medical School, New York. 111 pages with 54 illustrations. 1955, Grune & Stratton, Inc., New York and London. $4.50.

Several very good books on the subject of auscultation recently have been published, and this is another. It is obviously only an introduction. The material is clearly described, reduced to simplest terms, and freed of the speculative and the unproved. Traditional views have been rejected where they did not concur with the authors' experience.

Simultaneous auscultation and visualization by oscilloscope cannot, of course, be transmitted through a book. It might therefore be of great help if the reproduced stethograms which are unaccompanied by electrocardiograms were labeled minutely.

The format and illustrations are excellent.

W. S. B.

► SYSTEMIC ASSOCIATIONS AND TREATMENT OF SKIN DISEASES

By Kurt Wiener, M.D., Dermatologist, Mount Sinai Hospital, Milwaukee. 556 pages with 90 illustrations. 1955, The C. V. Mosby Company, St. Louis. $17.00.

This excellent treatise on skin manifestations of internal diseases is concerned with the relationship of dermatology and general medicine. The chapters on the systemic relationship of lupus erythematosus and scleroderma are particularly well written.

The material on systemic therapy of skin diseases presents a third aspect which one might call systemic therapy in dermatology. It includes not only the nontopical drugs but also indirect radiation therapy, diets, hormones and especially the use of spas.

The book is well organized and is especially good for practitioners of medicine who are interested in dermatology and dermatologists who are interested in medicine.

J. H. L.

(Continued on page A-116)

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► SURVEY OF CLINICAL PEDIATRICS

By Lawrence B. Slobody, M.D., Professor and Director of the Department of Pediatrics, New York Medical College, New York. Ed. 2. 502 pages. 1955, The Blakiston Division, McGraw-Hill Book Company, Inc., New York, Toronto and London. $9.50.

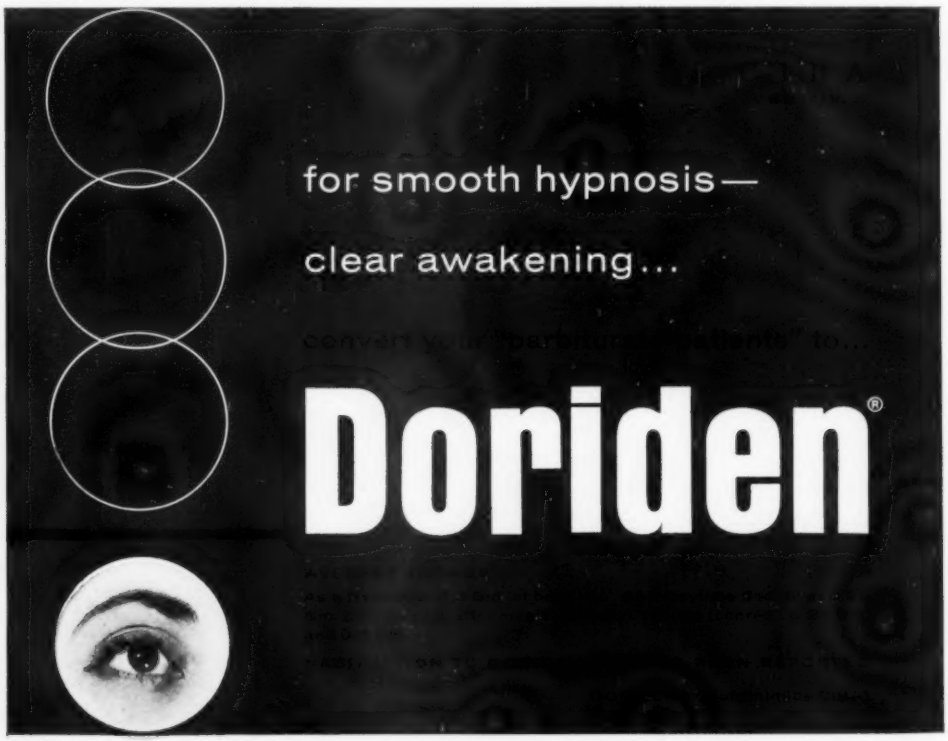
The second edition of this book is designed to focus attention on the high lights and relationships of pediatrics as encountered in clinical pediatric practice. The standard chapters on growth and development, the premature and newborn infant, and infant feeding appear, as well as chapters devoted to disorders of the various organ systems of the body. In addition, there are chapters on preventive pediatrics, psychologic problems, fluid and electrolyte balance, neoplasms in infancy and childhood, endocrine disorders and allergy. At the end of each section are questions to test one's knowledge of the preceding subject matter. These should prove helpful to the student preparing for examinations. References are provided at the end of the book for more comprehensive review of any particular subject.

This edition provides data on the newer antibotics and on chelating agents for lead poisoning. Viral diseases and abnormal hemoglobin are considered and new entities added such as cat scratch fever, familial dysautonomia, postmaturity, vitamin B_6 deficiency and agammaglobulinemia.

The problems of adoption are discussed, as are those of hospitalization and of reading disabilities, in line with the emphasis on consideration of the child as a whole. The author uses an outline form to avoid a didactic approach and tends toward the majority opinion on controversial subjects. The book includes many tables that are of value in presenting the material clearly and briefly. The work is not a substitute for the standard texts on pediatrics but, as its title indicates, is a survey of the clinical problems met in pediatric practice with concise information on their diagnoses and treatment.

S. D. M.

(Continued on page A-118)



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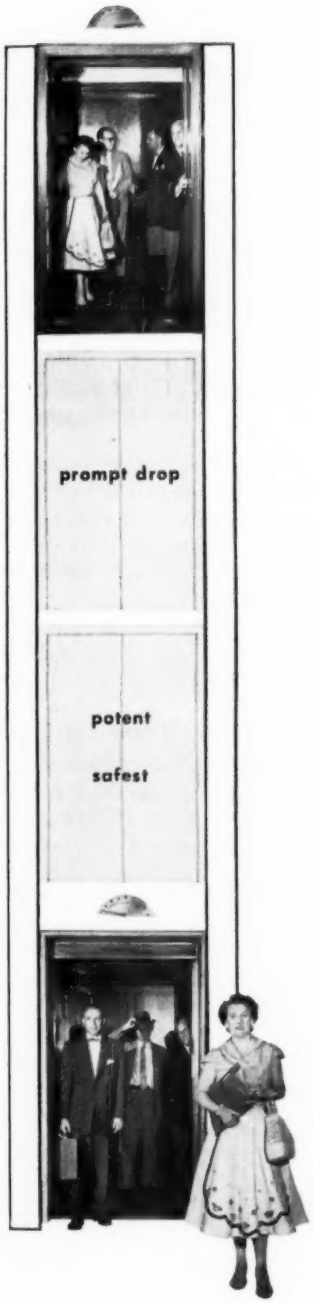

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*T.M.

► MANAGEMENT OF DISORDERS OF THE AUTONOMIC NERVOUS SYSTEM

By Louis T. Palumbo, M.D., Chief, Surgical Service, Veterans Administration Hospital, Des Moines. 186 pages. 1955, The Year Book Publishers, Inc., Chicago. $5.00.

The purpose of this general practice manual, as stated by the author, is to present in a simple, concise manner the present knowledge of the anatomy and physiology of the autonomic nervous system, and the application of this knowledge to the medical and surgical management of a variety of diseases.

The author set out to acquaint the general physician with various aspects of the autonomic nervous system, and he has accomplished his aim creditably. His style is attractive, and the text is understandable. Anatomic diagrams are simply drawn, and the illustrations are of satisfactory quality. A long bibliography is included.

Those chapters which are devoted to surgery of the autonomic system provide wide coverage of the subject within a short space. The general physician will find the section on the medical and surgical treatment of hypertension extremely interesting, pertinent and thought-provoking.

H. W. D.

► A TEXTBOOK OF MEDICINE

Edited by Russell L. Cecil, M.D., Professor of Clinical Medicine Emeritus, Cornell University, New York, and Robert F. Loeb, M.D., Bard Professor of Medicine, Columbia University, New York. With three associate editors. Ed. 9. 1,786 pages, illustrated. 1955, W. B. Saunders Company, Philadelphia and London. $15.00.

With the new ninth edition, "A Textbook of Medicine" continues to keep abreast of recent developments in medicine. Sections on 39 subjects which were not included in previous editions have been added, and many of the old sections have been revised and brought up to date. The very helpful section on normal laboratory values also has been expanded by the addition of many new items. These changes have made the new edition more than 150 pages longer than the previous edition. As before, Cecil and Loeb's "Textbook" is an outstanding book in its field.

R. V. R.

(Continued on page A-120)

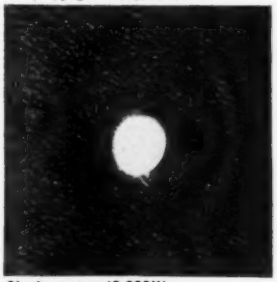
The organisms commonly involved in

Pneumonia

D. pneumoniae (10,000X)

K. pneumoniae (6,500X)

Strep. pyogenes (8,500X)



Staph. aureus (9,000X)

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► CLUES IN THE DIAGNOSIS AND TREATMENT OF HEART DISEASE

By Paul D. White, M.D., Consultant in Medicine, Massachusetts General Hospital, Boston. 186 pages with 35 illustrations. 1955, Charles C Thomas, Springfield, Illinois. $5.50.

One of the American Lecture Series, this book has been written primarily for the family physician or the general practitioner. Dr. White emphasizes the importance of the patient's history in diagnosis and, in particular, the specific problems of thoracic pain, breathlessness and palpitation. The remainder of the book discusses the important aspects of the physical examination as it pertains to the heart, and accessory clues to be obtained from roentgenography and electrocardiography. There are numerous reproductions of electrocardiograms and roentgenograms of the thorax to highlight and document the discussion. Most specialists, internists and cardiologists will find little that is new or helpful in this book, as it primarily offers basic clinical knowledge. Medical students and nonspecialists should find the book very helpful.

It is unfortunate that some important material had to be omitted from the text and was relegated to the appendix. It is also disquieting to notice misspelled words and mixed-up phrases, of which the most noticeable examples occur in the first four lines of page 163.

R. O. B.

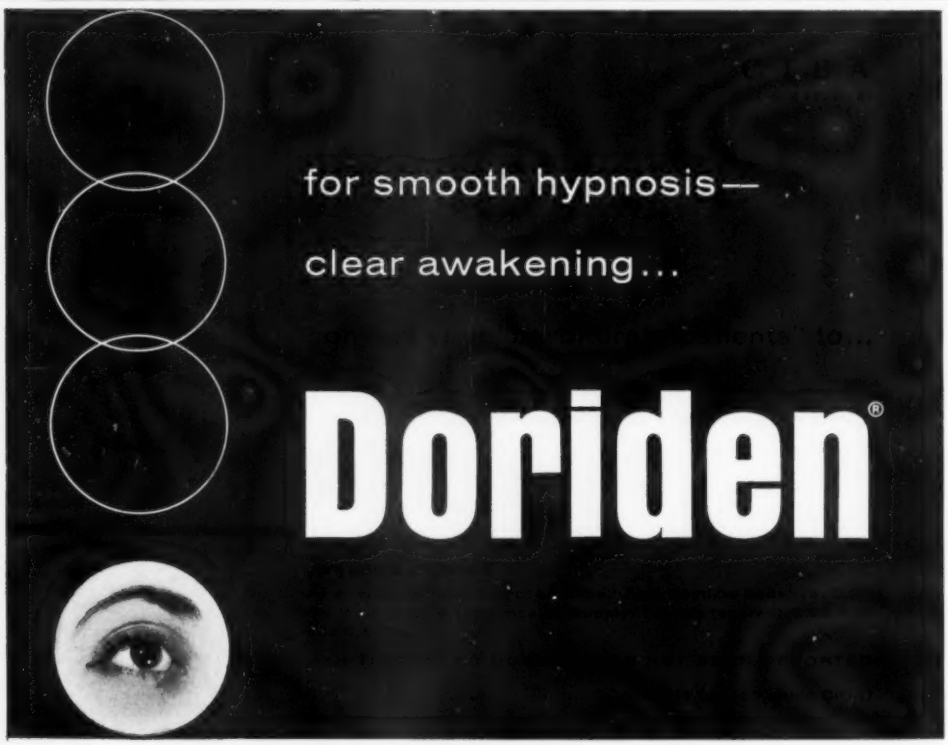
► TRANSPLANTATION OF TISSUES

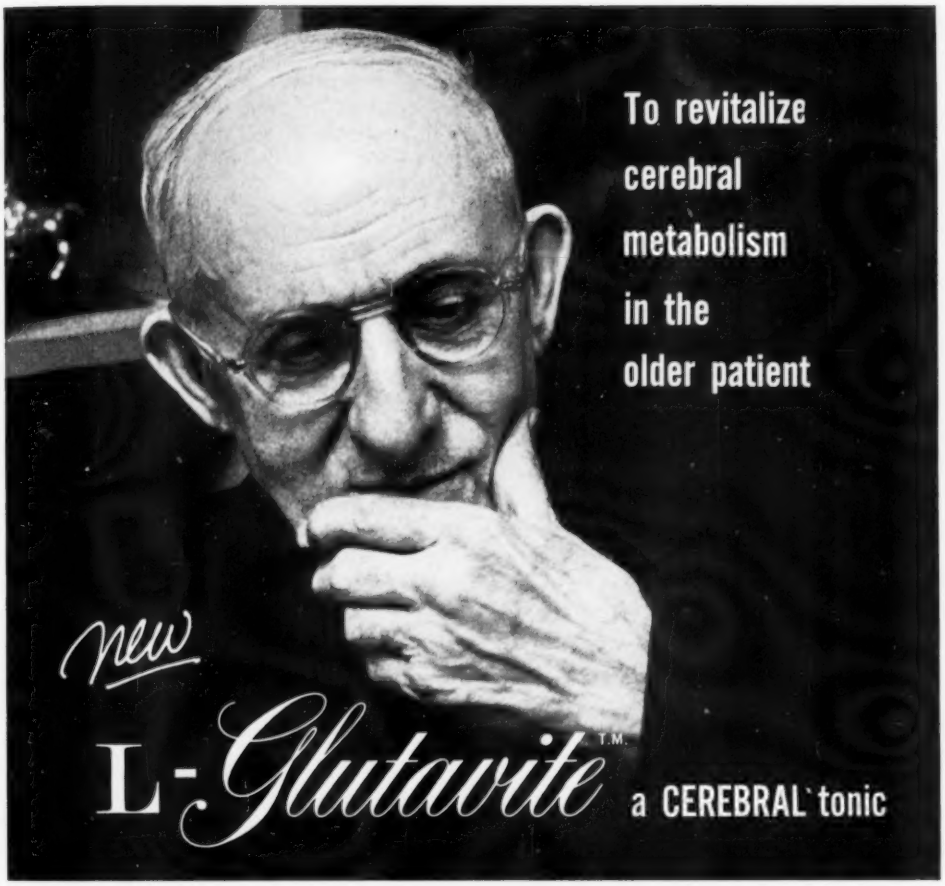
By Lyndon A. Peer, M.D., Clinical and Research Director, Rehabilitation Center for Plastic and Reconstructive Surgery, St. Barnabas Hospital, Newark, New Jersey. Vol. 1. 421 pages with 163 illustrations. 1955, The Williams & Wilkins Company, Baltimore. $13.50.

Believing that a need exists for a comprehensive treatise which covers the current literature on the research and clinical application relating to tissue transplantation, the author has completed volume 1 on this subject. He has covered the various aspects of cartilage, bone, fascia, tendon and muscle transplantation.

Dr. Peer, who has devised a number of original technics for tissue transplantation and plastic surgery, is well known in this field.

(Continued on page A-122)





L-Glutavite is specifically formulated to assist in the treatment of geriatric patients whose symptoms of weakness, apathy and fatigue are characteristic of waning cerebral metabolism. Himwich[1] reports excellent results with sodium glutamate in such cases, while Lehmann states that "a trial with nicotinic acid is always indicated . . ."[2] By combining these key factors with other vital nutritional elements, L-Glutavite effectively increases cerebral blood flow while it enhances the ability of cerebral tissue to utilize the increased nutrients provided. This unique therapeutic formula helps the tired, the apathetic, the depressed individual to face life more actively, and with greater interest.

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1. Himwich H.E.: Paper presented at American Psychiatric Association meeting, St. Louis, May, 1954.
2. Lehmann, H.: 27th Annual Conference, Milbank Memorial Fund, New York, Paul B. Hoeber, Inc., 1952. p. 587.

GP GRAY PHARMACEUTICAL CO., INC., Newton 58, Massachusetts

The first portion of the book is devoted to general considerations of tissue cells in their normal environment, at lowered temperatures and in a dehydrated environment, and the behavior of cells when transplanted as autologous, homologous and heterologous grafts.

Following this section are detailed and illustrated descriptions of the fate and the clinical applications of cartilage, bone, fascia, tendon and muscle transplants. The early literature on various phases of this problem is reviewed.

The last portion of this book is devoted to a discussion of the cell-survival versus replacement theories. From his detailed study of autogenetic free grafts of five basic tissues, namely, cartilage, bone, fascia, tendon and muscle, the author found that all grafts tend to survive and remain identifiable as the type of tissue transplanted, except muscle, which is always replaced by a fibrous tissue.

In homologous and heterologous tissue grafts, however, replacement by fibrous tissue of the host is uniform.

Increased application of tissue transplantation procedures in clinical surgery makes this book timely.

Y. S.

► DIFFERENTIAL DIAGNOSIS OF INTERNAL DISEASES

By Julius Bauer, M.D., Clinical Professor of Medicine, College of Medical Evangelists, Los Angeles. Ed. 2. 940 pages, illustrated. 1955, Grune & Stratton, Inc., New York and London. $15.00.

Differential diagnosis of the symptoms and signs associated with disease is covered in this volume. In the first half of the book, the author deals with the differential diagnosis of headache, thoracic pain, abdominal pain, vertigo, nausea, cough, dyspnea and other important symptoms. The second half includes discussion of the various signs that are found in diseases of the respiratory tract, cardiovascular system, gastrointestinal tract and other systems of the body.

The author repeatedly stresses the importance of functional complaints and their differentiation from organic disease. This is quite commendable, because most textbooks of medicine fail to include a discussion of symptoms of a functional nature despite the fact that functional complaints make up a large part of any physician's practice.

(Continued on page A-126)

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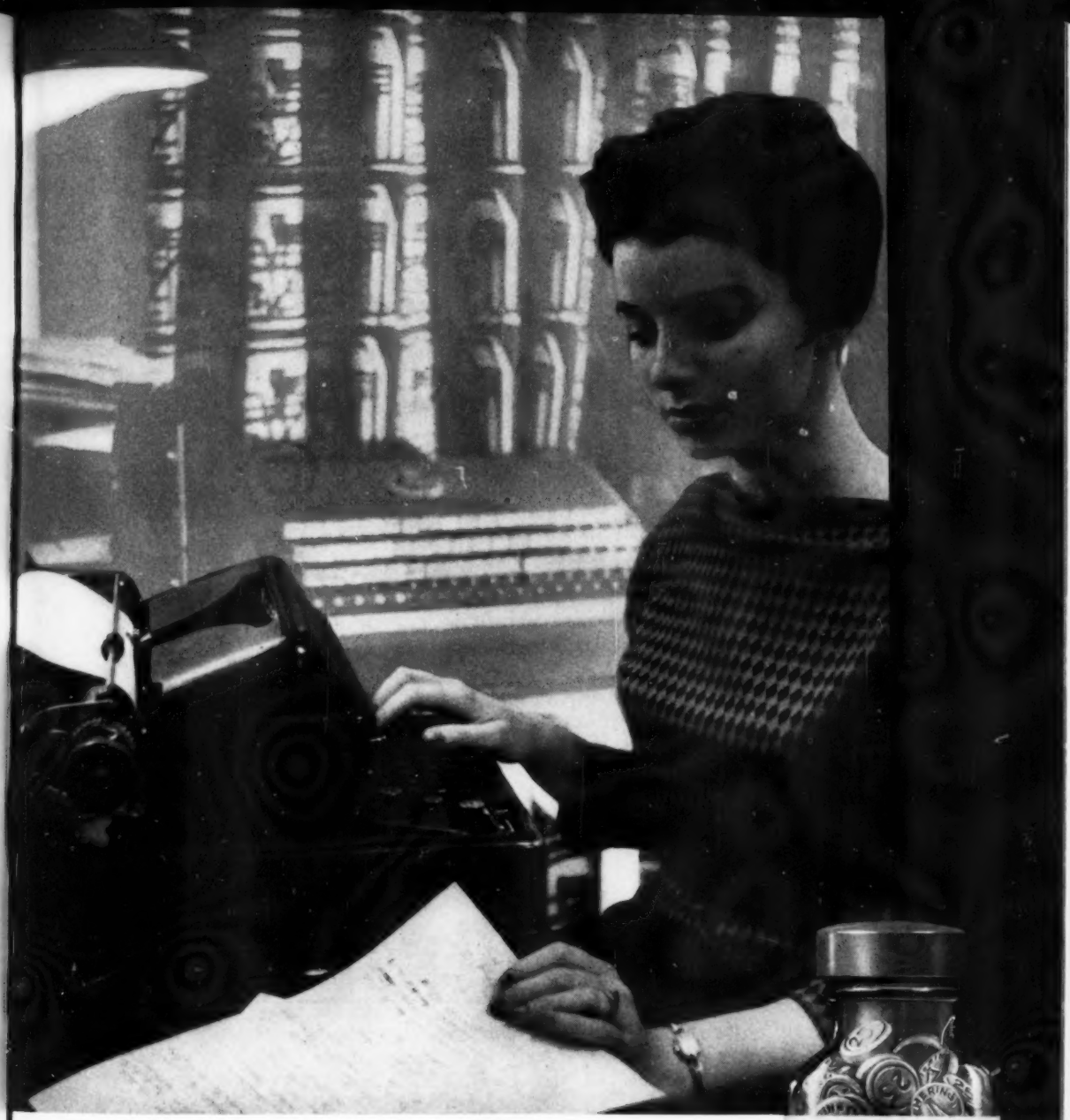

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*Parsons, L., and Tenny, B., Jr.: M. Clin. North America *34*:1537, 1950.

CL-J-51

The text is enhanced by many brief case reports, photographs and reproductions of roentgenograms. As the author predicts in the preface, some of his views will not be shared by others. However, in general, the contents of this book are based on sound concepts and should prove helpful to all physicians doing diagnostic work.

R. V. R.

► PRACTITIONERS' CONFERENCES

Edited by Claude E. Forkner, M.D., Professor of Clinical Medicine, Cornell University Medical College, New York. Vol. 1. 411 pages. 1955, Appleton-Century-Crofts, Inc., New York. $6.75.

In volume 1 of this series Dr. Forkner has initiated a program of interest to the general practitioner. The term general practitioner may be a misnomer because he is a doctor of medicine who renders service, sometimes in a limited capacity, in surgery or pediatrics and some of the other specialties. It is this type of practicing physician who may not have time to study the intricate and detailed chemical and physiologic alterations involved in disease processes. If these can be summarized by experts in these fields in a manner that the practicing physician can understand, this undoubtedly can become a unique educational program. A great deal of postgraduate medical education is confined to doctors within a teaching institution; however, Dr. Forkner has invited the doctors in the community who are not members of the teaching institution to come to and participate, if necessary, in discussing various subjects of interest. This enables doctors in the community to ask questions regarding their practices and to learn of the most recent advancements in the management and therapy of a disease process.

The present volume includes discussions of such subjects as influenza and primary atypical pneumonia, asthma, the present status of ACTH and cortisone, the harmful effects of tobacco, the home treatment of acute poliomyelitis, headache, acidosis, and diabetes mellitus. Experts in medicine, physiologists, pathologists and bacteriologists express their points of view. Questions are asked by the panelists as well as by physicians in the audience. Finally, a résumé by Dr. Forkner resolves the discussion. There are references at the end of each chapter.

S. A. L.

(Continued on page A-128)

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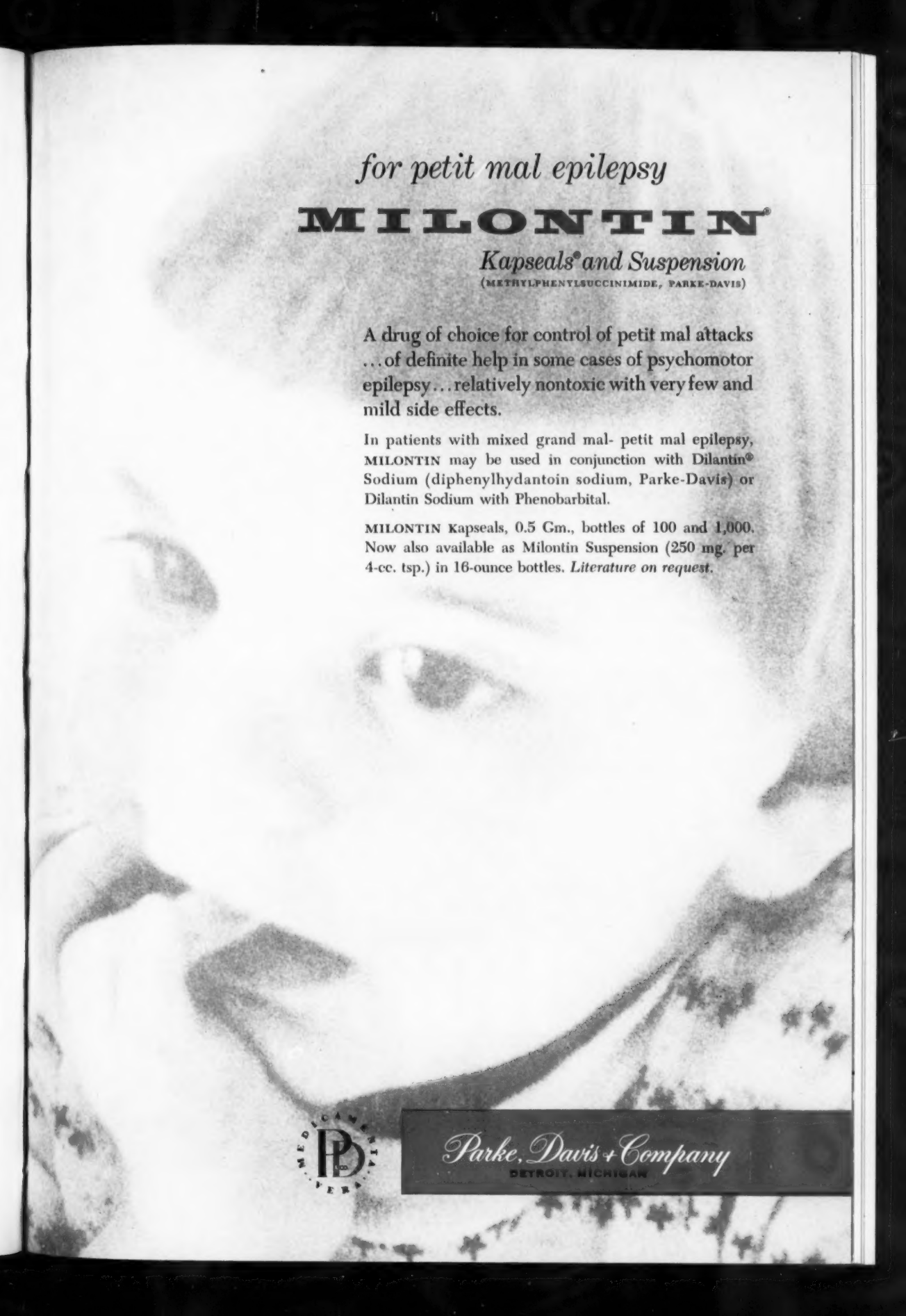

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► PATHOLOGY FOR THE SURGEON

By William Boyd, M.D., Lecturer on the Humanities in Medicine, The University of Toronto, Toronto, Canada. Ed. 7. 737 pages with 574 illustrations. 1955, W. B. Saunders Company, Philadelphia and London. $12.50.

The name of this excellent work has been changed and the contents rewritten and markedly altered to keep pace with the rapid advancements in medicine and surgery today. Of particular interest are the tables of contents at the beginning of each chapter. By this means the author provides a splendid classification of the material contained therein. Considerable pathologic physiology has been incorporated, and many new chapters have been added on infections of wounds, and on the skin, the endocrine glands and the cardiovascular system.

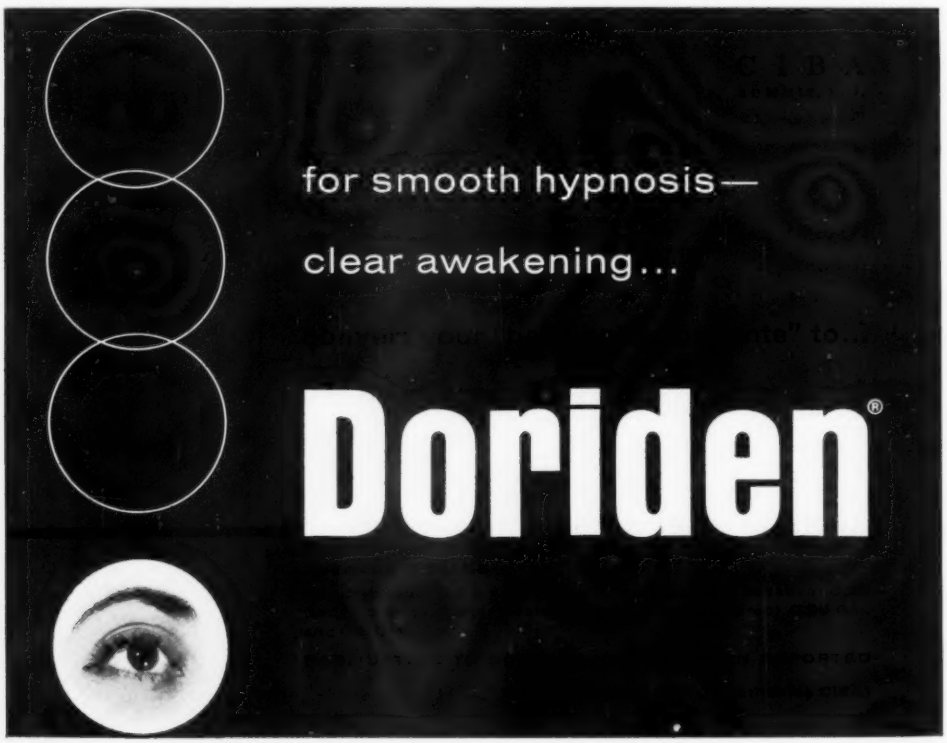
The sections on the gastrointestinal tract have been particularly well done, and the pertinent physiologic data which accompany them lend a completeness seldom found.

This is also true of the sections on the cardiovascular system and the lungs and mediastinum, as well as the rapidly expanding associated fields.

W. H. R.

► DIFFERENTIAL DIAGNOSIS OF LEUKOPLAKIA, LEUKOKERATOSIS AND CANCER IN THE MOUTH

By Ashton L. Welsh, M.D., Assistant Professor of Dermatology and Syphilology, University of Cincinnati College of Medicine, Cincinnati. 62 pages. 1955, Charles C Thomas, Springfield, Illinois. $2.50.

Three phases of the problem of leukoplakia, leukokeratosis, and cancer in the mouth are presented in this small opus. Dr. Welsh discusses leukoplakia as a precancerous dermatosis, then leukokeratosis as a term used to designate an advanced stage of leukoplakia, and, finally, its termination in the form of a cancer. He discusses the early and later lesions, the etiology of leukoplakia, mentioning the various irritants that may be precursors to the development of leukoplakia in the mouth, the advanced stage of leukoplakia which is a leukokeratosis, the early and later lesions, the histopathology, and various types of squamous cell carcinoma which is the end result of leukoplakia. He also mentions clinical pathologic entities which may simulate leukoplakia and should be considered in the diagnosis.

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